

**Title Page**

<b>Protocol Title:</b>		A Phase 3 Japanese Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention								
<b>Short Protocol Title:</b>		A Phase 3 Japanese Randomized Controlled Trial of Erenumab in Migraine Prevention								
<b>Protocol Number:</b>		20170609								
<b>Investigational Product:</b>		AMG 334 (erenumab)								
<b>Sponsor</b>	<b>Name of Sponsor:</b>	Amgen Inc.								
	<b>Address:</b>	One Amgen Center Drive Thousand Oaks, CA 91320, USA								
	<b>Telephone Number:</b>	+1 (805) 447-1000								
<b>Key Sponsor Contact</b>	<b>Name:</b>	[REDACTED]								
	<b>Address:</b>	One Amgen Center Drive Thousand Oaks, CA 91320, USA								
	<b>Telephone Number:</b>	[REDACTED]								
	<b>Email Address:</b>	[REDACTED]								
<b>EudraCT Number:</b>		Not applicable								
<b>NCT Number:</b>		<b>NCT03812224</b>								
<b>Protocol Date:</b>		<table border="0"> <thead> <tr> <th><u>Document Version</u></th> <th><u>Date</u></th> </tr> </thead> <tbody> <tr> <td>Original</td> <td>10 September 2018</td> </tr> <tr> <td>Amendment 1</td> <td>19 December 2018</td> </tr> <tr> <td><b>Amendment 2</b></td> <td><b>02 December 2019</b></td> </tr> </tbody> </table>	<u>Document Version</u>	<u>Date</u>	Original	10 September 2018	Amendment 1	19 December 2018	<b>Amendment 2</b>	<b>02 December 2019</b>
<u>Document Version</u>	<u>Date</u>									
Original	10 September 2018									
Amendment 1	19 December 2018									
<b>Amendment 2</b>	<b>02 December 2019</b>									
<b>Version/Date:</b>		<u>Data Element Standards Version</u> 6.1								

Approved

### **Confidentiality Notice**

This document contains confidential information of Amgen Inc.

This document must not be disclosed to anyone other than the site study staff and members of the institutional review board/independent ethics committee/institutional scientific review board or equivalent.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: US sites, 1- 800-77-AMGEN; Canadian sites, 1-866-50-AMGEN; for all other countries, 1-805-447-1000; Amgen's general number in the US, 1-805-447-1000.

Approved

**Investigator's Agreement:**

I have read the attached protocol entitled A Phase 3 Japanese Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention, dated **02 December 2019**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse [or legal partner] and dependent children) and my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of Investigator

\_\_\_\_\_  
Date (DD Month YYYY)

Approved

## Table of Contents

Table of Contents .....	4
1. Protocol Synopsis.....	10
2. Study Schema and Schedule of Activities.....	14
2.1 Study Schema .....	14
2.2 Schedule of Activities .....	15
3. Introduction .....	24
3.1 Study Rationale .....	24
3.2 Background .....	24
3.2.1 Disease.....	24
3.2.2 Amgen Investigational Product Background: Erenumab.....	25
3.3 Benefit/Risk Assessment.....	25
3.3.1 Therapeutic Context .....	26
3.3.2 Key Benefits .....	26
3.3.3 Key Risks.....	26
3.3.3.1 Risks .....	28
4. Objectives, Endpoints and Hypotheses.....	28
4.1 Objectives and Endpoints.....	28
4.2 Hypotheses.....	31
5. Study Design .....	31
5.1 Overall Design .....	31
5.2 Number of Subjects .....	32
5.2.1 Replacement of Subjects.....	32
5.2.2 Number of Sites.....	32
5.3 End of Study .....	32
5.3.1 End of Study Definition .....	32
5.3.2 Study Duration for Subjects.....	33
5.4 Justification for Investigational Product Dose.....	33
5.5 Patient Input on Study Design .....	36
5.6 Definitions of Terms Included in Endpoints .....	36
6. Study Population .....	37
6.1 Inclusion Criteria Part 1 .....	38
6.2 Exclusion Criteria Part 1 .....	38
6.3 Inclusion Criteria Part 2 .....	41
6.4 Exclusion Criteria Part 2 .....	41
6.5 Subject Enrollment .....	42
6.6 Screen Failures .....	43
7. Treatments .....	43

7.1	Treatment Procedures.....	43
7.1.1	Investigational Products .....	43
7.1.2	Non-investigational Products.....	45
7.1.3	Medical Devices .....	45
7.1.4	Other Protocol-required Therapies .....	45
7.1.5	Other Treatment Procedures.....	45
7.1.6	Product Complaints .....	45
7.1.7	Excluded Treatments, Medical Devices, and/or Procedures During Study Period.....	46
7.2	Method of Treatment Assignment .....	47
7.3	Blinding.....	47
7.3.1	Site Personnel Access to Individual Treatment Assignments.....	47
7.3.2	Access to Individual Subject Treatment Assignments by Amgen or Designees .....	47
7.4	Dose Modification .....	48
7.4.1	Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation.....	48
7.4.2	Hepatotoxicity Stopping and Rechallenge Rules.....	48
7.5	Preparation/Handling/Storage/Accountability .....	48
7.6	Treatment Compliance .....	48
7.7	Treatment of Overdose.....	49
7.8	Prior and Concomitant Treatment .....	49
7.8.1	Prior Treatment.....	49
7.8.2	Concomitant Treatment.....	49
8.	Discontinuation Criteria .....	49
8.1	Discontinuation of Study Treatment .....	50
8.2	Discontinuation From the Study .....	51
8.2.1	Reasons for Removal From Washout, Run-in or Invasive Procedures.....	51
8.2.2	Reasons for Removal From Study .....	51
8.3	Lost to Follow-up .....	51
9.	Study Assessments and Procedures .....	52
9.1	General Study Periods .....	52
9.1.1	Screening, Enrollment and/or Randomization .....	52
9.1.1.1	Screening Period and Baseline Period .....	52
9.1.1.2	Randomization .....	53
9.1.2	Treatment Period.....	53
9.1.3	Early Termination .....	53
9.1.4	Safety Follow-up.....	53
9.1.5	End of Study .....	53
9.2	Description of General Study Assessments and Procedures.....	53

9.2.1	General Assessments .....	53
9.2.1.1	Informed Consent .....	53
9.2.1.2	Calls to Interactive Response Technology (IRT) System.....	54
9.2.1.3	Demographics.....	54
9.2.1.4	Medical History .....	54
9.2.1.5	Physical Examination.....	54
9.2.1.6	Physical Measurements.....	54
9.2.1.7	Hepatitis Testing .....	55
9.2.1.8	Urine Drug Screening .....	55
9.2.2	Efficacy Assessments.....	55
9.2.2.1	Clinical Outcome Assessments .....	55
9.2.2.6	Beck Depression Inventory .....	57
9.2.3	Safety Assessments .....	57
9.2.3.1	Adverse Events.....	58
9.2.3.2	Vital Signs .....	61
9.2.3.3	Electrocardiograms .....	61
9.2.3.4	Suicidal Risk Monitoring.....	62
9.2.3.5	Other Safety.....	62
9.2.4	Clinical Laboratory Assessments .....	62
9.2.4.1	Pregnancy Testing .....	63
9.2.4.2	Prespecified Biomarker Assessments .....	63
9.2.5	Pharmacokinetic Assessments.....	63
9.2.7	Antibody Testing Procedures .....	64
9.2.9	Clinical Outcome Assessments .....	65
9.2.10	Optional Substudies .....	65
9.2.11	Other Assessments .....	66
10.	Statistical Considerations .....	66
10.1	Sample Size Determination .....	66
10.2	Analysis Sets, Subgroups, and Covariates .....	67
10.2.1	Analysis Sets .....	67
10.2.2	Covariates .....	67
10.2.3	Subgroups .....	68
10.2.4	Handling of Missing and Incomplete Data .....	68
10.3	Statistical Analyses.....	69

10.3.1	Planned Analyses.....	69
10.3.1.1	Primary Analysis .....	69
10.3.1.2	Final Analysis.....	69
10.3.2	Methods of Analyses .....	69
10.3.2.1	General Considerations .....	69
10.3.2.2	Efficacy Analyses.....	70
10.3.2.3	Safety Analyses .....	70
11.	References.....	72
12.	Appendices .....	74
12.1	Appendix 1. List of Abbreviations and Definitions of Terms .....	75
12.2	Appendix 2. Clinical Laboratory Tests .....	78
12.3	Appendix 3. Study Governance Considerations.....	80
	Independent Review Committee .....	80
	Regulatory and Ethical Considerations .....	80
	Informed Consent Process .....	81
	Data Protection/Subject Confidentiality .....	82
	Publication Policy .....	83
	Investigator Signatory Obligations.....	84
	Data Quality Assurance.....	84
	Source Documents .....	85
	Study and Site Closure.....	86
	Compensation .....	87
12.4	Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting .....	88
	Definition of Adverse Event .....	88
	Definition of Serious Adverse Event.....	89
	Definition of Adverse Device Effect .....	90
	Recording Adverse Events, Disease-related Events (if applicable), and Serious Adverse Events.....	90
	Evaluating Adverse Events and Serious Adverse Events .....	91
	Reporting of Serious Adverse Event .....	92
12.5	Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information.....	96
	Definition of Females of Childbearing Potential.....	96
	Collection of Pregnancy Information.....	97
	Collection of Lactation Information .....	99
12.6	Appendix 6. Sample Storage and Destruction.....	102
12.7	Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines.....	104

Approved

	Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity.....	104
	Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity.....	105
	Drug-induced Liver Injury Reporting and Additional Assessments.....	106
12.8	Appendix 8. Substudy: Qualitative Interview Substudy to “A Phase 3 Japanese Randomized, Double Blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention”.....	108
	Substudy Background and Rationale .....	108
	Research Question and Objective(s) of the Qualitative Interview Substudy .....	108
	Substudy Design .....	108
	Summary of Substudy Subject Participation Criteria.....	109
	Substudy Duration and Substudy Procedures.....	109
	Variables .....	111
	Substudy Sample Size .....	111
	Substudy Data Analysis.....	111
	Collection of Safety Information and Product Complaints .....	112

#### List of Tables

Table 2-1.	Schedule of Activities – Study Visits Through Double-blind Treatment Period .....	15
Table 2-2.	Schedule of Activities - Study Visits Through Open-label Treatment Period and Safety Follow-up .....	20
Table 2-3.	Schedule of Activities – Optional Interview-based Substudy .....	23
Table 3-1.	Adverse Reactions With Erenumab .....	27
Table 5-1.	Treatment-emergent Adverse Events Occurring in $\geq 2\%$ of Subjects in the All Erenumab Group in the Double-blind Treatment Period by Preferred Term (Safety Analysis Set).....	34
Table 5-2.	Treatment-emergent Adverse Events Occurring in $\geq 2\%$ of Subjects in the All Erenumab Group, Preferred Term (Safety Analysis Set).....	36
Table 7-1.	Study Treatments.....	44
Table 10-1.	Likelihood of Observing Greater MMD Reduction in Erenumab 70 mg Compared to Placebo in the EM/CM Subgroup.....	67
Table 12-1.	Analyte Listing.....	79
Table 12-2.	Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity .....	105



---

**List of Figures**

Figure 2-1. Study Schema ..... 14

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Form ..... 93

Figure 12-2. Pregnancy and Lactation Notification Worksheets ..... 100

Approved

## 1. Protocol Synopsis

**Protocol Title:** A Phase 3 Japanese Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention

**Short Protocol Title:** A Phase 3 Japanese Randomized Controlled Trial of Erenumab in Migraine Prevention

**Study Phase:** 3

**Indication:** Prevention of Migraine

### Rationale

Migraine prevention is an area of a large unmet medical need, with existing therapies often having modest efficacy and poor tolerability. Calcitonin gene-related peptide (CGRP) receptor antagonism is a novel approach to migraine preventive therapy. Erenumab is a human monoclonal antibody against canonical CGRP receptor. The present study is a phase 3 confirmatory trial intended to assess the efficacy and safety of erenumab for prevention of migraine in Japanese subjects with episodic migraine (EM) and chronic migraine (CM).

### Objective(s)/Endpoint(s)

Objectives	Endpoints
<b>Primary</b>	
<ul style="list-style-type: none"><li>To evaluate the effect of erenumab compared to placebo on the change from baseline in mean monthly migraine days (MMD)</li></ul>	<ul style="list-style-type: none"><li>Change from baseline in mean MMD over months 4, 5, and 6 of the double-blind treatment period (DBTP)</li></ul>
<b>Primary Estimand</b>	
<p>The primary estimand consists of:</p> <ul style="list-style-type: none"><li>The target population, which is Japanese subjects diagnosed with migraine who were randomized, received at least one dose of investigational product, and had at least 1 change from baseline measurement in MMD during the DBTP.</li><li>The primary endpoint, which is the change from baseline in mean MMD over months 4, 5, and 6 of the DBTP.</li><li>The summary measure, which is the mean difference of the primary endpoint between AMG 334 70 mg and placebo groups.</li><li>The intercurrent event, adherence to treatment will be ignored and the primary endpoint will be assessed for all subjects in the target population regardless of adherence to treatment.</li></ul>	
<b>Secondary</b>	
<ul style="list-style-type: none"><li>To evaluate the effect of erenumab compared to placebo on the proportion of subjects with at least a 50% reduction from baseline in mean MMD</li></ul>	<ul style="list-style-type: none"><li>Achievement of at least a 50% reduction from baseline in mean MMD over months 4, 5, and 6 of the DBTP</li></ul>
<ul style="list-style-type: none"><li>To evaluate the effect of erenumab compared to placebo on the change from baseline in mean monthly acute migraine-specific medication treatment days</li></ul>	<ul style="list-style-type: none"><li>Change from baseline in mean monthly acute migraine-specific medication treatment days over months 4, 5, and 6 of the DBTP</li></ul>

Objectives	Endpoints
<b>Safety</b>	
<ul style="list-style-type: none"><li>To evaluate the safety and tolerability of erenumab</li></ul>	<ul style="list-style-type: none"><li>Subject incidence of treatment-emergent adverse events</li><li>Clinical laboratory values and vital signs</li><li>Subject incidence of anti-erenumab antibodies</li></ul>

## Hypotheses

In subjects with migraine, erenumab treatment results in a greater reduction from baseline in mean monthly migraine days (MMD), compared to placebo.

## Overall Design

This is a phase 3, randomized, double-blind, placebo-controlled study of subjects with EM or CM. The planned length of participation in the study for an individual is up to 67 weeks, which includes the following:

- An initial screening period (up to 3 weeks)
- 4-week baseline period
- 24-week DBTP
- 28-week open-label treatment period (OLTP)
- 8-week safety follow-up period (12 weeks after the last dose of investigational product)

Subjects will be randomized in 1:1 allocation ratio to erenumab or placebo, respectively.

The randomization will be performed by **IRT** and subjects will be stratified by EM/CM and migraine preventive treatment status (ever used [prior and/or current] or never used).

## Number of Subjects

Approximately 256 subjects (including approximately 156 EM and 100 CM subjects) will be enrolled in the study, with approximately 128 subjects randomized to erenumab 70 mg and 128 subjects randomized to placebo (in each arm, approximately 78 subjects with EM and 50 subjects with CM).

## Summary of Subject Eligibility Criteria

Japanese subjects  $\geq 20$  to  $\leq 65$  years of age with a history of migraine (with or without aura) for  $\geq 12$  months before screening and who experience CM or EM over the 3 months before screening.

For a full list of eligibility criteria, please refer to [Section 6.1](#) to [Section 6.4](#).

## Treatments

Investigational product (ie, erenumab and/or placebo) will be dosed every 4 weeks (Q4W), subcutaneously (SC). Double-blind erenumab 70 mg or placebo will be administered during the 24-week DBTP (ie, at day 1 and weeks 4, 8, 12, 16, and 20) and erenumab 70 mg will be administered during the 28-week OLTP (ie, at weeks 24, 28, 32, 36, 40, 44, and 48). Erenumab will be packaged as 70 mg in 1 mL prefilled syringes. Placebo prefilled syringes will be packaged to match erenumab but will not contain erenumab.

Investigational product doses are fixed and will not be adjusted for individual subjects during the study. The anatomical sites for administration of investigational product are the upper arm, upper thigh, or abdomen.

## Procedures

After signing informed consent, subjects will enter the screening period. The screening period is composed of an initial screening period (up to 3 weeks) followed by a 4-week baseline period. At the day 1 visit following the baseline period, eligible subjects will be randomized into the 24-week DBTP and will begin to receive double-blind investigational product Q4W SC. At the week 24 visit, subjects in each treatment group will begin to receive open-label erenumab 70 mg for the 28-week OLTP. A safety follow-up visit will occur 12 weeks after the last dose of investigational product, which can occur during the DBTP or OLTP. Subjects will have scheduled in-clinic study visits monthly from week -4 through the end of the OLTP.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product through the safety follow-up visit or end of study, whichever is later, are reported using the Event case report form (CRF).

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the safety follow-up visit or end of study, whichever is later, are reported using the Event CRF.

All serious adverse events will be collected, recorded, and reported to the sponsor or designee within 24 hours. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

For a full list of study procedures, including the timing of each procedure, please refer to [Section 9.2](#) and the Schedule of Activities in [Table 2-1](#) and [Table 2-2](#).

## Statistical Considerations

The primary analysis will be performed when the last subject completes the assessments for week 24 or the early termination (ET) visit during the DBTP. The final analysis will be performed after all subjects have completed safety follow-up at the end of the study.

The treatment effect and variability are weighted based on treatment effect and variability estimates from Japanese EM Study 20120309 and pivotal global CM Study 20120295. Randomizing 256 subjects (128 subjects per treatment group, approximately 78 for EM and 50 for CM) will account for 10% dropout.

Continuous efficacy endpoints will be analyzed using the repeated measures linear mixed effects model including treatment group, baseline values, stratification factors, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation of missing data beyond proration of electronic diary (eDiary) data per [Section 10.2.4](#) under the missing-at-random (MAR) assumption on missing data mechanism. The least squares means (LSM) change from baseline with the 95% CI for each treatment group, the treatment difference (erenumab 70 mg - placebo) with the 95% CI, and p-value will be reported.

Dichotomous efficacy endpoints will be analyzed using a stratified Cochran Mantel Haenszel (CMH) test after the missing data are imputed as non-response. The odds

ratio for erenumab 70 mg group versus placebo group, associated 95% CI, and p-value will be reported.

As safety analyses, subject incidence of treatment-emergent adverse events will be tabulated by treatment group and by system organ class and preferred term.

Measurements of safety, laboratory, and vital sign data will be summarized over time by treatment group and laboratory shift tables will be provided. All safety analyses will be performed for the DBTP and the OLTP separately.

For a full description of statistical analysis methods, please refer to [Section 10](#).

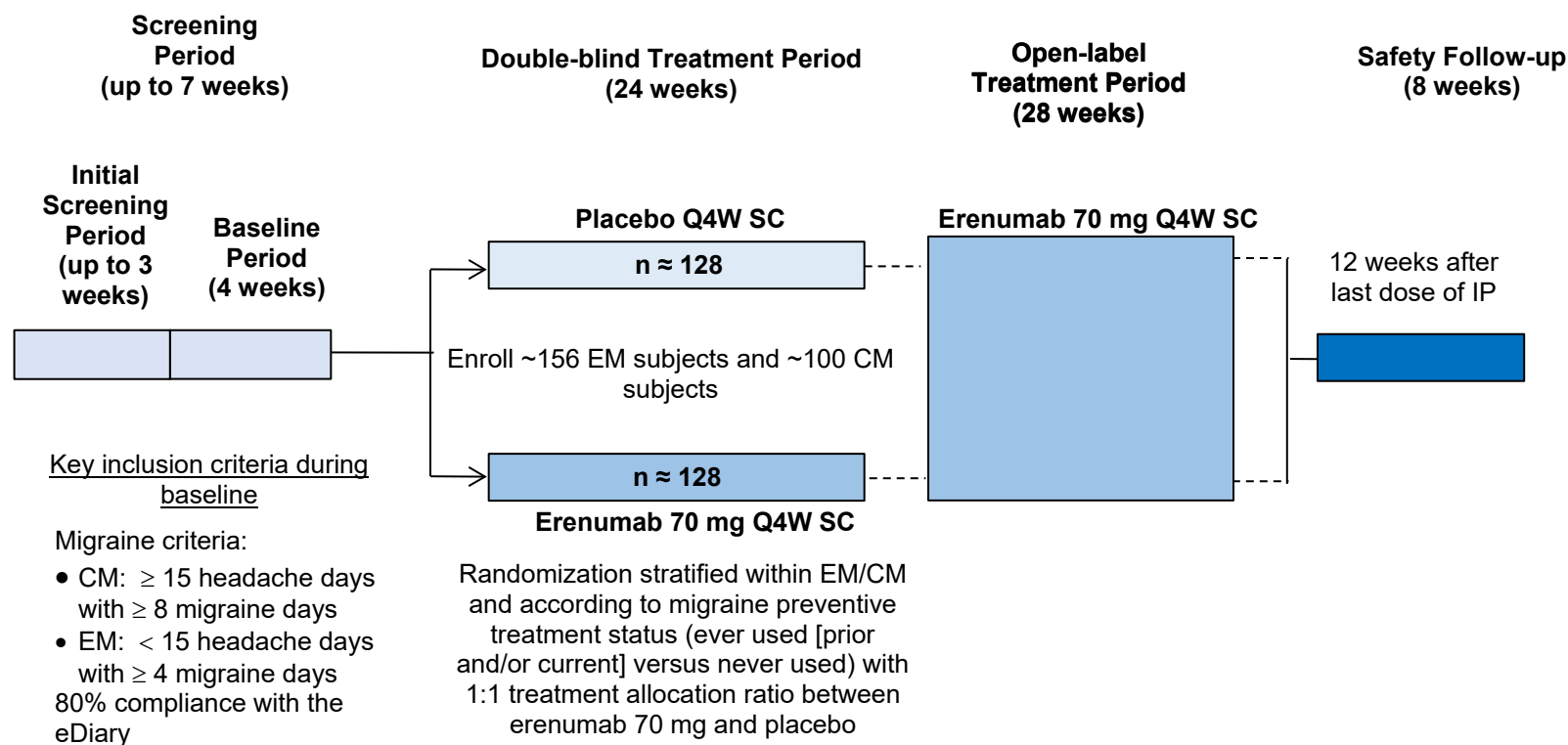
**Sponsor Name:** Amgen Inc.

Approved

## 2. Study Schema and Schedule of Activities

### 2.1 Study Schema

Figure 2-1. Study Schema



CM = chronic migraine; EM = episodic migraine; eDiary = electronic diary; IP = investigational product; Q4W = every 4 weeks; SC = subcutaneously.

## 2.2 Schedule of Activities

**Table 2-1. Schedule of Activities – Study Visits Through Double-blind Treatment Period**

Procedure	Screening Period (up to 7 wks)		Double-blind Treatment Period (24 wks) <sup>a</sup>							Follow-up
	Initial Screening (up to 3 wks)	Baseline Period (4 wks) <sup>a</sup>	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ ET <sup>b</sup>	Safety (12 wks after last dose in DBTP if subject does not enter OLTP)/End of Study
		Wk -4								
GENERAL AND SAFETY ASSESSMENTS										
Informed consent	X									
Calls to <b>IRT</b> system	X		X	X	X	X	X	X	X	X
Entry into the baseline period		X								
Inclusion and exclusion criteria	X		X							
Randomization into the double-blind treatment period <sup>c</sup>			X							
Demographics	X									
Physical examination	X									X
Physical measurements	X		X						X	
Medical and medication history	X									
Hepatitis B and C sample collection	X									
ECG	X		X	X	X	X			X	

Footnotes defined on last page of table.

Page 1 of 4

**Table 2-1. Schedule of Activities – Study Visits Through Double-blind Treatment Period**

Procedure	Screening Period (up to 7 wks)		Double-blind Treatment Period (24 wks) <sup>a</sup>							Follow-up
	Initial Screening (up to 3 wks)	Baseline Period (4 wks) <sup>a</sup>	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ ET <sup>b</sup>	Safety (12 wks after last dose in DBTP if subject does not enter OLTP)/End of Study
		Wk -4								
GENERAL AND SAFETY ASSESSMENTS CONT.										
Vital signs	X	X	X	X	X	X	X	X	X	X
Adverse event collection/recording/reporting			X	X	X	X	X	X	X	X
Serious adverse event collection/recording/reporting <sup>d</sup>	X	X	X	X	X	X	X	X	X	X
Adverse device effects			X	X	X	X	X	X	X	X
Product complaints recording			X	X	X	X	X	X	X	X
Prior/concomitant medications recording			X	X	X	X	X	X	X	X
LABORATORY ASSESSMENTS										
Urine drug screen	X	Testing as needed throughout study based on investigator's clinical suspicion								
Serum pregnancy test (females of childbearing potential only) – Central lab	X									X
Urine pregnancy test (females of childbearing potential only) – Local lab			X	X	X	X	X	X	X	
Chemistry, hematology	X		X	X		X			X	X

Page 2 of 4

Footnotes defined on last page of table.



**Table 2-1. Schedule of Activities – Study Visits Through Double-blind Treatment Period**

Procedure	Screening Period (up to 7 wks)		Double-blind Treatment Period (24 wks) <sup>a</sup>							Follow-up
	Initial Screening (up to 3 wks)	Baseline Period (4 wks) <sup>a</sup>	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ ET <sup>b</sup>	Safety (12 wks after last dose in DBTP if subject does not enter OLTP)/End of Study
		Wk -4								
LABORATORY ASSESSMENTS CONT.										
Urinalysis	X								X	
Anti-erenumab antibody; serum			X	X		X			X	X
STUDY-SPECIFIC ASSESSMENTS										
Site assigns eDiary to subject		X								
Subject brings eDiary to site for use during study visit			X	X	X	X	X	X	X	
PHARMACOKINETIC ASSESSMENTS										
PK sampling (collected predose)			X	X	X	X			X	
CLINICAL OUTCOME ASSESSMENTS										
Daily diary		X (daily)								
C-SSRS	X	X	X	X	X	X	X	X	X	X

Footnotes defined on last page of table.

Page 3 of 4

**Table 2-1. Schedule of Activities – Study Visits Through Double-blind Treatment Period**

Procedure	Screening Period (up to 7 wks)		Double-blind Treatment Period (24 wks) <sup>a</sup>							Follow-up
	Initial Screening (up to 3 wks)	Baseline Period (4 wks) <sup>a</sup>	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ ET <sup>b</sup>	Safety (12 wks after last dose in DBTP if subject does not enter OLTP)/End of Study
		Wk -4								
CLINICAL OUTCOME ASSESSMENTS CONT.										
BDI-2	X		X						X	
STUDY TREATMENT										
Amgen investigational product administration <sup>f</sup>			X	X	X	X	X	X		

Footnotes defined on last page of table.

Page 4 of 4

BDI-2 = Beck Depression Inventory 2; COAs = Clinical Outcome Assessments; C-SSRS = Columbia-suicide Severity Rating Scale; DBTP = double-blind treatment period; ECG = electrocardiogram; eDiary = electronic diary; ET = early termination; [REDACTED] IRT = interactive **response technology**; [REDACTED] OLTP = open-label treatment period; Wk = week.

<sup>a</sup> Each study visit during the double-blind treatment period (DBTP) and safety follow-up visit has a window of  $\pm 3$  consecutive calendar days. The day 1 visit (randomization day) has a window of 0, +7 consecutive calendar days; the day 1 visit must occur 28 to 35 days after the week -4 visit date. All study visit target dates are to be calculated from the day 1 visit date. All study procedures for a given study visit are to be completed on the same day.

<sup>b</sup> A subject who discontinues the study during the DBTP will complete the week 24/early termination (ET) visit.

<sup>c</sup> Randomization and administration of the first dose of investigational product should occur on day 1.

<sup>d</sup> Serious adverse events are to be collected after signing of the informed consent through end of study (12 weeks after the last dose of investigational product). Non-serious adverse events are to be collected after the first dose of investigational product through end of study (12 weeks after the last dose of investigational product).

<sup>f</sup> Administration of investigational product is to be administered last during each visit that it is required.

Approved

**Table 2-2. Schedule of Activities - Study Visits Through Open-label Treatment Period and Safety Follow-up**

Procedure	Open-label Treatment Period (28 wks) <sup>a</sup>								Follow-up <sup>a</sup>
	Wk 24 (cont.)	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52/ET <sup>b</sup>	Safety (12 wks after last dose in OLTP)/End of Study
<b>GENERAL AND SAFETY ASSESSMENTS</b>									
Calls to IRT system	X	X	X	X	X	X	X	X	X
Entry into the OLTP <sup>c</sup>	X								
Physical examination									X
Body weight measurement								X	X
ECG								X	
Vital signs		X	X	X	X	X	X	X	X
Adverse event collection/recording/reporting	X	X	X	X	X	X	X	X	X
Serious adverse event collection/recording/reporting <sup>d</sup>	X	X	X	X	X	X	X	X	X
Adverse device effects	X	X	X	X	X	X	X	X	X
Product complaints recording	X	X	X	X	X	X	X	X	X
Concomitant medications recording		X	X	X	X	X	X	X	X
<b>LABORATORY ASSESSMENTS</b>									
Urine drug screen	Testing as needed throughout study based on investigator's clinical suspicion								

Footnotes defined on last page of table.

Page 1 of 3

**Table 2-2. Schedule of Activities - Study Visits Through Open-label Treatment Period and Safety Follow-up**

Procedure	Open-label Treatment Period (28 wks) <sup>a</sup>								Follow-up <sup>a</sup>
	Wk 24 (cont)	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52/ET <sup>b</sup>	Safety (12 wks after last dose in OLTP)/End of Study
LABORATORY ASSESSMENTS CONT.									
Serum pregnancy test (females of childbearing potential only) – Central lab									X
Urine pregnancy test (females of childbearing potential only) – Local lab		X	X	X	X	X	X	X	
Chemistry, hematology								X	X
Anti-erenumab antibody; serum		X		X				X	X
STUDY-SPECIFIC ASSESSMENTS									
Subject brings eDiary to site for use during study visit		X	X	X	X	X	X	X	
PHARMACOKINETIC ASSESSMENTS									
PK sampling (collected predose)		X		X				X	
CLINICAL OUTCOME ASSESSMENTS									
Daily diary			X (daily from weeks 33 to 36)				X (daily from weeks 49 to 52)		
C-SSRS		X	X	X	X	X	X	X	X

Page 2 of 3

Footnotes defined on last page of table.

**Table 2-2. Schedule of Activities - Study Visits Through Open-label Treatment Period and Safety Follow-up**

Procedure	Open-label Treatment Period (28 wks) <sup>a</sup>								Follow-up <sup>a</sup>
	Wk 24 (cont)	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52/ET <sup>b</sup>	Safety (12 wks after last dose in OLTP)/End of Study
<b>CLINICAL OUTCOME ASSESSMENTS Cont.</b>									
<b>STUDY TREATMENT</b>									
Amgen investigational product administration <sup>f</sup>	X	X	X	X	X	X	X		

Page 3 of 3

COAs = Clinical Outcome Assessments; C-SSRS = Columbia-suicide Severity Rating Scale; DBTP = double-blind treatment period; ECG = electrocardiogram; eDiary = electronic diary; ET = early termination; [REDACTED]; IRT = interactive **response technology**; [REDACTED]

[REDACTED]; OLTP = open-label treatment period; PK = pharmacokinetic; Wk = week

<sup>a</sup> Each study visit during the open-label treatment period (OLTP) has a window of  $\pm 4$  consecutive calendar days. The safety follow-up visit has a window of  $\pm 3$  consecutive calendar days. All study visit target dates are to be calculated from the day 1 visit date. All study procedures for a given study visit are to be completed on the same day.

<sup>b</sup> A subject who discontinues open-label investigational product or the study during the OLTP will complete the week 52/early termination (ET) visit.

<sup>c</sup> Entry into the OLTP using the **IRT** System must occur only after completion of all DBTP procedures and prior to the first dose of open-label erenumab

<sup>d</sup> Serious adverse events are to be collected after signing of the informed consent through end of study (12 weeks after the last dose of investigational product). Non-serious adverse events are to be collected after the first dose of investigational product through end of study (12 weeks after the last dose of investigational product).

<sup>f</sup> Administration of investigational product is to be administered last during each visit that it is required.

**Table 2-3. Schedule of Activities – Optional Interview-based Substudy**

Procedure	Week 48-52	Week 52
Substudy informed consent	X <sup>a</sup>	
Substudy Participation Requirements	X <sup>a</sup>	
Interview <sup>b</sup>		X

<sup>a</sup> Signing of informed consent and participation screening can occur any time at or after the Week 48 visit.

<sup>b</sup> Interviewers will attempt to conduct the interview as soon as possible and within 10 business days after Week 52 visit.

Approved

### **3. Introduction**

#### **3.1 Study Rationale**

Migraine prevention is an area of a large unmet medical need, with existing therapies often having modest efficacy and poor tolerability. Calcitonin gene-related peptide (CGRP) receptor antagonism is a novel approach to migraine preventive therapy. Erenumab is a human monoclonal antibody against canonical CGRP receptor. The present study is a phase 3 confirmatory trial intended to assess the efficacy and safety of erenumab for prevention of migraine in Japanese subjects with episodic migraine (EM) and chronic migraine (CM).

The current study was designed according to the principles outlined in the European Medicines Agency (EMA) Guideline on Clinical Investigation of Medicinal Products for the Treatment of Migraine (CHMP/EWP/788/01 Rev. 1), the International Headache Society (IHS) Guidelines for Controlled Trials of Drugs in Migraine ([Tassorelli et al, 2018](#); [Tfelt-Hansen et al, 2012](#)) and based on scientific advice obtained from the Pharmaceuticals and Medical Devices Agency (PMDA).

#### **3.2 Background**

##### **3.2.1 Disease**

##### **Migraine**

Migraine is a disabling disorder characterized by primary recurrent headaches with or without aura lasting 4 to 72 hours with at least 2 of the following pain characteristics: unilateral, pulsating, moderate or severe intensity, or aggravated by routine physical activity. In addition, the migraine attacks are often accompanied by nausea, vomiting, and sensitivity to light (photophobia) and sound (phonophobia).

Migraine is a highly prevalent disease worldwide. The prevalence of migraine is approximately 11.7% in the USA, 14.6% in Canada, 14.7% in Europe, and 8.4% in Japan ([Stovner and Andree, 2010](#); [Lipton et al, 2007](#); [Sakai and Igarashi, 1997](#)).

Depending on the headache frequency, migraine is divided into 2 broad forms: episodic migraine (EM) and chronic migraine (CM) [ICHD 3]. Episodic migraine is characterized by migraine with fewer than 15 headache days per month, while CM is characterized by 15 or more headache days per month (where at least 8 of those days are migraine days). Episodic migraine and CM share many common features in terms of the clinical presentation, which include the headache pain features and associated symptoms. Although EM and CM are somewhat arbitrarily distinguished based on migraine headache frequency, numerous lines of evidence support that they are a continuum of



the same disorder. Not only are clinical symptomologies and functional impairments very similar, but functional imaging results demonstrating that similar areas of the brain are involved support a common underlying pathophysiology ([Aurora and Wilkinson, 2007](#); [Afridi et al, 2005](#); [Aurora et al, 2005](#); [Welch et al, 2001](#)). Only approximately 12% of patients receive any preventive therapy due to limited efficacy and significant tolerability and safety issues with available preventive therapies. Migraine prevention is an area of large unmet medical need.

### **3.2.2 Amgen Investigational Product Background: Erenumab**

The study drug, erenumab, is a genetically recombinant drug manufactured using Chinese hamster ovary (CHO) cell line. Erenumab is a human immunoglobulin G2 (IgG2) that is directed against the canonical CGRP receptor complex and inhibits the action of CGRP. Calcitonin gene-related peptide belongs to the calcitonin family of peptides and is expressed in both the central and peripheral nervous systems. It is prominently involved in the pathophysiology of migraine through nociceptive modulation, in the trigeminovascular system ([Goadsby et al, 2002](#); [Tajti et al, 1999](#)). Nonclinical studies with erenumab demonstrated that it binds to and antagonizes both human and cynomolgus monkey CGRP receptors with high affinity and potency. Erenumab has been developed for the prevention of migraine in adults based on the observed long serum half-life in humans (28 days), clinical data demonstrating that small molecule CGRP receptor antagonists are effective in acute migraine reversal ([Ho et al, 2008a](#); [Ho et al, 2008b](#)), prevention ([Ho et al, 2014](#)), and the strong rationale for CGRP's association with migraine pathophysiology ([Goadsby et al, 2017](#); [Sun et al, 2016](#); [Bellamy et al, 2006](#); [Sarchielli et al, 2006](#); [Juhasz et al, 2005](#); [Petersen et al, 2005](#); [Lassen et al, 2002](#); [Tajti et al, 1999](#); [Gallai et al, 1995](#); [Goadsby et al, 1990](#); [Goadsby et al, 1988](#)).

As of the date of approval of this protocol, erenumab 70 mg and 140 mg subcutaneously (SC) every 4 weeks (Q4W) or once monthly (QM) have been approved in the United States (US), Europe, Australia, and Switzerland for the prevention of migraine in adults.

A detailed description of the chemistry, pharmacology, efficacy, and safety of erenumab is provided in the [Investigator's Brochure](#).

### **3.3 Benefit/Risk Assessment**

The following benefit risk assessment supports the conduct of this clinical trial.

Reference should be made to the Investigator's Brochure for further data on erenumab.

### **3.3.1 Therapeutic Context**

The overall prevalence of migraine in Japan has been estimated to be 8.4% of the population (Sakai and Igarashi, 1997). Seventy-four percent (74%) of migraine patients feel daily life disturbance. However, in Japan, only a small number of preventive therapies are currently indicated for migraine, and the available options are insufficient. Moreover, prevention strategies for migraine are frequently based on literature published in North America and Europe (Shimizu, 2009). An international cross-sectional survey of adults with migraine revealed low rates of preventive therapy use due to discontinuation either because of lack of efficacy and/or adverse events (Blumenfeld et al, 2013).

### **3.3.2 Key Benefits**

Globally, the totality of results from the 2 pivotal studies in CM (Study 20120295, [including the open-label extension Study 20130255]) and EM (Study 20120296) provides substantial evidence for the efficacy and safety of erenumab in adults with migraine. For Japan, the evidence is further supported by the Japanese EM Study 20120309, which demonstrated a statistically significant reduction in change from baseline over months 4, 5, and 6 in monthly migraine days (MMD) for erenumab 70 mg versus placebo with a least squares means (LSM; 95% CI) versus placebo of -2.3 (-3.0, -1.6) days. Significantly more subjects in the erenumab 70 mg group achieved at least a 50% reduction in MMD from baseline over months 4, 5, and 6 compared to placebo (20% versus 7%, respectively). Furthermore, there was a statistically significant greater reduction in change from baseline in mean monthly acute migraine-specific medication treatment days over months 4, 5, and 6 in the erenumab 70 mg group versus placebo, with a LSM (95% CI) versus placebo of -2.07 (-2.66, -1.49) days in the erenumab 70 mg group. The key benefits of erenumab consist of results that include reduction in frequency of MMDs, reduction in acute migraine-specific medication use, [REDACTED]

[REDACTED] Patient-reported Outcome [PRO]), as well as improvements in a range of other PROs, favorable tolerability (over the standard of care), low treatment discontinuation rates, convenience (QM injections with the option of self-administration), and rapid onset of effect.

### **3.3.3 Key Risks**

As of the time of the marketing application in the US and European Union, 2057 subjects with migraine were exposed to erenumab 70 mg or 140 mg QM for at least 6 months, 1198 subjects were exposed for at least 12 months, and 287 subjects were exposed for

at least 18 months. In 3 placebo-controlled clinical studies (Studies 20120295, 20120296, and 20120297) of 2184 patients, 787 patients received at least one dose of erenumab 70 mg QM, 507 patients received at least one dose of erenumab 140 mg once monthly, and 890 patients received placebo during 3 months or 6 months of double-blind treatment.

The most common adverse reactions in the migraine studies were injection site reactions and constipation. [Table 3-1](#) summarizes all adverse reactions that occurred in erenumab-treated subjects during the 12-week placebo-controlled period of the pooled trials. Most adverse drug reactions were mild or moderate in severity.

**Table 3-1. Adverse Reactions With Erenumab**

<b>System Organ Class</b>	<b>Adverse Reaction Preferred Term</b>	<b>Frequency Category</b>	<b>Overall Subject Incidence at 70 mg (N = 893) n (%)</b>	<b>Overall Subject Incidence at 140 mg (N = 507) n (%)</b>	<b>Placebo Subject Incidence (N = 1043) n (%)</b>	<b>Nature/Severity/Seriousness of Erenumab Arms</b>
General disorders and administration site conditions	injection site reactions <sup>a</sup>	Common	50 (5.6) <sup>a</sup>	23 (4.5) <sup>a</sup>	33 (3.2) <sup>a</sup>	
Gastrointestinal disorders	constipation	Common	12 (1.3)	16 (3.2)	11 (1.1)	
Musculoskeletal and connective tissue disorders	muscle spasm	Common <sup>d</sup>	1 (0.1)	10 (2.0)	4 (0.4)	One grade 3 (0.2%) event was reported; all others were grade 1 or 2 <sup>b</sup>
Skin and subcutaneous tissue disorders	pruritus <sup>c</sup>	Common <sup>d</sup>	6 (0.7) <sup>c</sup>	9 (1.8) <sup>c</sup>	5 (0.5)	

Note: Frequency is provided by Council for International Organizations of Medical Sciences category (eg, Very Common ( $\geq 10\%$ ), Common ( $\geq 1\%$  and  $< 10\%$ ), uncommon ( $\geq 0.1\%$  and  $< 1\%$ ), rare ( $\geq 0.01\%$  and  $< 0.1\%$ ), very rare ( $< 0.01\%$ )).

<sup>a</sup> Injection site reactions includes multiple preferred terms, such as injection site pain and injection site erythema.

<sup>b</sup> Severity grades are based on the Common Terminology Criteria for Adverse Events (CTCAE). Grade 1 mild; grade 2 moderate; grade 3 severe or medically significant; grade 4 life-threatening consequences; grade 5 death.

<sup>c</sup> Pruritus includes preferred terms of generalized pruritus, pruritus, and pruritic rash.

<sup>d</sup> Frequency category is based on the highest frequency for either the 70 mg or 140 mg doses.

In the 3 placebo-controlled migraine studies, 1.3% and 1.1% of patients treated with erenumab (70 mg or 140 mg) or placebo, respectively, discontinued double-blind treatment because of adverse events.

### 3.3.3.1 Risks

There is no important identified risk or important potential risk with erenumab. The safety and efficacy of erenumab has not been established in migraine patients with major cardiovascular disease (myocardial infarction [MI], stroke, transient ischemic attack [TIA], unstable angina, coronary artery bypass surgery, or other revascularization procedures within 12 months prior to screening), in the long-term use of erenumab, or in elderly patients > 65 years of age.

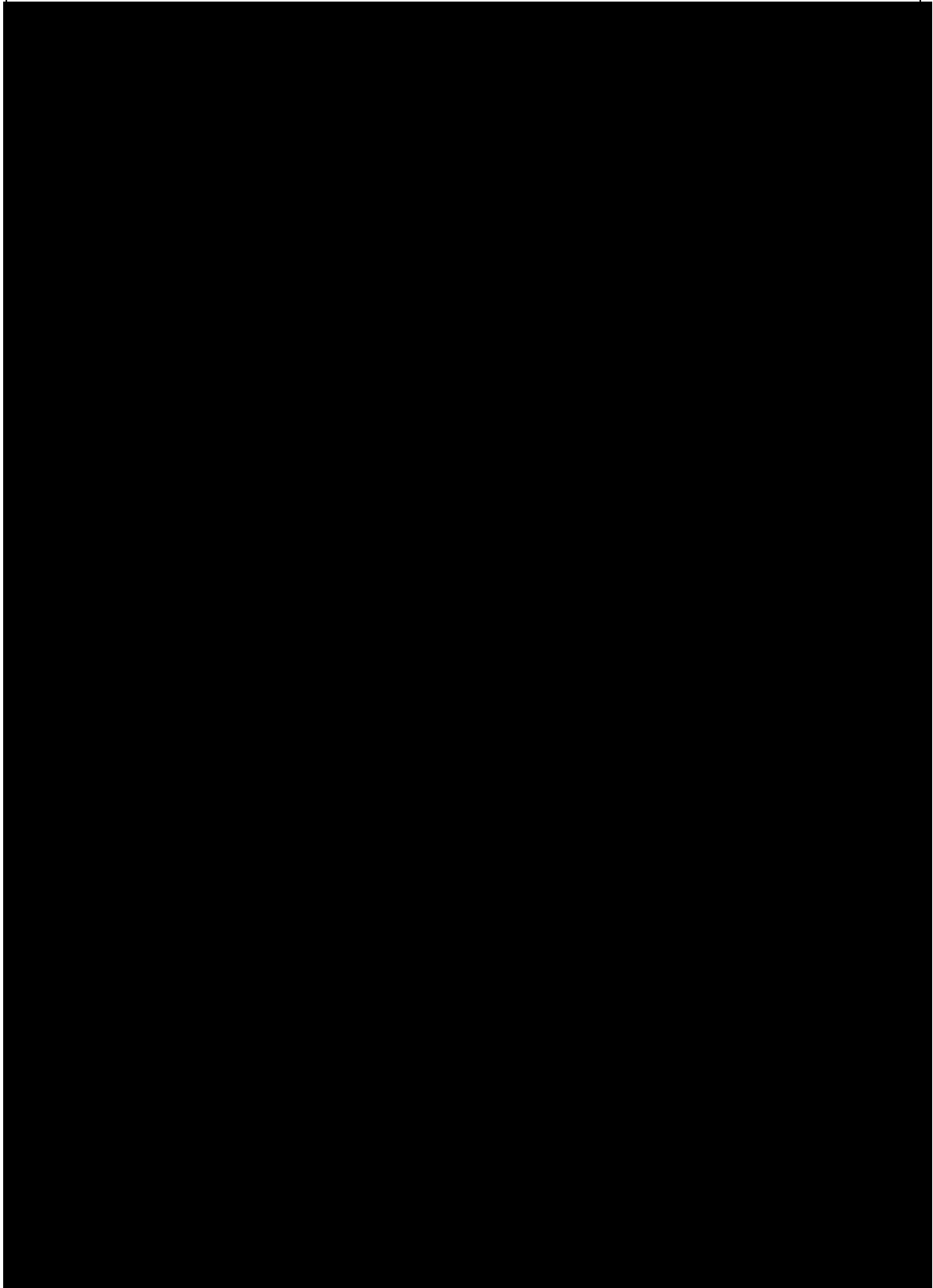
## 4. Objectives, Endpoints and Hypotheses

### 4.1 Objectives and Endpoints

Objectives	Endpoints
<b>Primary</b>	
<ul style="list-style-type: none"> <li>To evaluate the effect of erenumab compared to placebo on the change from baseline in mean monthly migraine days (MMD)</li> </ul>	<ul style="list-style-type: none"> <li>Change from baseline in mean MMD over months 4, 5, and 6 of the double-blind treatment period (DBTP)</li> </ul>
<b>Primary Estimand</b>	
<p>The primary estimand consists of:</p> <ul style="list-style-type: none"> <li>The target population, which is Japanese subjects diagnosed with migraine who were randomized, received at least one dose of investigational product, and had at least 1 change from baseline measurement in MMD during the DBTP.</li> <li>The primary endpoint, which is the change from baseline in mean MMD over months 4, 5, and 6 of the DBTP.</li> <li>The summary measure, which is the mean difference of the primary endpoint between AMG 334 70 mg and placebo groups.</li> <li>The intercurrent event, adherence to treatment will be ignored and the primary endpoint will be assessed for all subjects in the target population regardless of adherence to treatment.</li> </ul>	
<b>Secondary</b>	
<ul style="list-style-type: none"> <li>To evaluate the effect of erenumab compared to placebo on the proportion of subjects with at least a 50% reduction from baseline in mean MMD</li> </ul>	<ul style="list-style-type: none"> <li>Achievement of at least a 50% reduction from baseline in mean MMD over months 4, 5, and 6 of the DBTP</li> </ul>
<ul style="list-style-type: none"> <li>To evaluate the effect of erenumab compared to placebo on the change from baseline in mean monthly acute migraine-specific medication treatment days</li> </ul>	<ul style="list-style-type: none"> <li>Change from baseline in mean monthly acute migraine-specific medication treatment days over months 4, 5, and 6 of the DBTP</li> </ul>
<b>Safety</b>	
<ul style="list-style-type: none"> <li>To evaluate the safety and tolerability of erenumab</li> </ul>	<ul style="list-style-type: none"> <li>Subject incidence of treatment-emergent adverse events</li> <li>Clinical laboratory values and vital signs</li> <li>Subject incidence of anti-erenumab antibodies</li> </ul>

Approved

Objectives	Endpoints
Exploratory	



Approved

Objectives	Endpoints
Exploratory (continued)	

--	--

Approved

Objectives	Endpoints
Exploratory (continued)	

## 4.2 Hypotheses

In subjects with migraine, erenumab treatment results in a greater reduction from baseline in mean MMD, compared with placebo.

## 5. Study Design

### 5.1 Overall Design

This is a phase 3, randomized, double-blind, placebo-controlled study in subjects with EM or CM.

The study is composed of an initial screening period (up to 3 weeks), a 4-week baseline period, a 24-week DBTP, a 28-week open-label treatment period (OLTP), and an 8-week safety follow-up period (12 weeks after the last dose of investigational product).

Subjects will have scheduled in-clinic study visits monthly from week -4 through the end of the OLTP.

Approximately 256 eligible subjects (including approximately 156 EM and 100 CM subjects) will be randomized 1:1 to erenumab 70 mg or placebo (in each arm, approximately 78 subjects with EM and 50 subjects with CM).

Randomization will occur when the subject meets all baseline eligibility criteria and prior to the first investigational product administration in the DBTP. Randomization will be stratified by EM/CM and migraine preventive treatment status (ever used [prior and/or current] or never used).

Investigational product (ie, placebo or erenumab) will be dosed Q4W, SC.

The overall study design is described by a study schema in [Section 2.1](#). The endpoints are defined in [Section 4.1](#).

## **5.2 Number of Subjects**

Participants in this clinical investigation shall be referred to as “subjects”. Approximately 256 subjects (including approximately 156 EM and 100 CM subjects) will be enrolled in the study, with approximately 128 subjects randomized to erenumab 70 mg and 128 subjects randomized to placebo (in each arm, approximately 78 subjects with EM and 50 subjects with CM).

For the sample size justification, see [Section 10.1](#).

### **5.2.1 Replacement of Subjects**

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

### **5.2.2 Number of Sites**

Approximately 40 investigative sites in Japan will be included in the study. Sites that do not enroll subjects within 3 months of site initiation may be closed.

## **5.3 End of Study**

### **5.3.1 End of Study Definition**

**Primary Completion:** The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

The primary completion date is the date when the last subject has completed the assessments for week 24 or is discontinued from the study.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

**End of Study:** The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.



### **5.3.2 Study Duration for Subjects**

The planned length of participation in the study for an individual subject is up to 67 weeks, which includes the following:

- screening period (up to 3 weeks)
- 4-week baseline period
- 24-week DBTP
- 28-week OLTP
- 8-week safety follow-up period (12 weeks after the last dose of investigational product)

### **5.4 Justification for Investigational Product Dose**

Erenumab 70 mg will be evaluated in the present study. Subjects will receive either erenumab 70 mg or placebo Q4W SC for 24 weeks in the DBTP, followed by a 28-week OLTP during which all subjects will receive erenumab 70 mg Q4W SC. The rationale for the dose is based on results from the Japan phase 2 EM Study 20120309 and the global pivotal CM Study 20120295.

Study 20120309 randomized Japanese EM subjects to receive placebo, erenumab 28, 70, or 140 mg in a 2:1:2 ratio over a 24-week DBTP. There was a statistically significant greater reduction in the change from baseline in mean MMD over the last 3 months (months 4, 5, and 6) of the DBTP for erenumab 28, 70, and 140 mg compared to placebo. The difference in LSM (95% CI) versus placebo was -1.25 (-2.10, -0.41) days, -2.31 (-3.00, -1.62) days and -1.89 (-2.58, -1.20) days for erenumab 28, 70, and 140 mg, respectively ( $p = 0.004$  for 28 mg,  $p < 0.001$  for 70 mg and 140 mg). The proportion of subjects who achieved at least a 50% reduction in mean MMD from baseline over the last 3 months (months 4, 5, and 6) of the DBTP was 7.4%, 19.7%, 28.9%, and 27.2% for the placebo, erenumab 28, 70, and 140 mg groups, respectively; results were statistically significant for each erenumab group versus placebo ( $p = 0.009$  for 28 mg,  $p < 0.001$  for 70 mg and 140 mg). Furthermore, for the endpoint of change from baseline in mean monthly acute migraine-specific medication treatment days over the last 3 months (months 4, 5, and 6) of the DBTP, the difference in LSM (95% CI) versus placebo was -1.07 (-1.80, -0.35) days, -2.07 (-2.66, -1.49) days, and -2.04 (-2.63, -1.45) days for erenumab 28, 70, and 140 mg, respectively ( $p = 0.004$  for 28 mg,  $p < 0.001$  for 70 mg and 140 mg).

During the DBTP, treatment-emergent adverse events were reported in 67.6%, 60.6%, 70.4%, and 69.3% of subjects for the placebo, erenumab 28, 70, and 140 mg groups,

respectively. The percentage of subjects with a serious adverse event was 2.9%, 1.5%, 0.7%, and 0.7% in the placebo, erenumab 28, 70, and 140 mg treatment groups, respectively. In the placebo group, 1 subject (0.7%) had an adverse event leading to withdrawal of investigational product, while 2 subjects (1.5%) in the erenumab 70 mg group had adverse events leading to withdrawal of investigational product. No subject in the erenumab 28 mg and 140 mg groups had an adverse event leading to withdrawal of investigational product. No fatal treatment-emergent adverse events were reported. The most common events ( $\geq 2\%$  of subjects in all erenumab groups combined) are listed in [Table 5-1](#).

**Table 5-1. Treatment-emergent Adverse Events Occurring in  $\geq 2\%$  of Subjects in the All Erenumab Group in the Double-blind Treatment Period by Preferred Term (Safety Analysis Set)**

Preferred Term	Placebo (N = 136) n (%)	Erenumab			
		28 mg (N = 66) n (%)	70 mg (N = 135) n (%)	140 mg (N = 137) n (%)	All erenumab (N = 338) n (%)
Number of subjects reporting treatment-emergent adverse events	92 (67.6)	40 (60.6)	95 (70.4)	95 (69.3)	230 (68.0)
Nasopharyngitis	40 (29.4)	22 (33.3)	39 (28.9)	45 (32.8)	106 (31.4)
Constipation	2 (1.5)	0 (0.0)	6 (4.4)	7 (5.1)	13 (3.8)
Pharyngitis	3 (2.2)	3 (4.5)	5 (3.7)	3 (2.2)	11 (3.3)
Back pain	2 (1.5)	3 (4.5)	7 (5.2)	1 (0.7)	11 (3.3)
Dental caries	3 (2.2)	2 (3.0)	6 (4.4)	2 (1.5)	10 (3.0)
Gastroenteritis	4 (2.9)	2 (3.0)	2 (1.5)	5 (3.6)	9 (2.7)
Abdominal pain upper	1 (0.7)	1 (1.5)	5 (3.7)	2 (1.5)	8 (2.4)

% =  $n/N \times 100$ ; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the analysis set; n = number of subjects reporting at least one occurrence of an adverse event in that class. Coded using MedDRA version 20.1.  
Source: Study 20120309 Primary Analysis CSR.

In Study 20120309, the frequencies of adverse events, serious adverse events, and adverse events leading to discontinuation of investigational product were similar across the placebo, erenumab 28, 70, and 140 mg treatment groups during the DBTP. Overall, with the exception of constipation which occurred at a higher incidence in the erenumab 70 mg and 140 mg dose groups compared with either placebo or erenumab 28 mg treatment group, there were no notable differences in the incidence, severity, or nature

of adverse events between the treatment groups (placebo and All erenumab). There were no other significant dose-dependent adverse events.

Study 20120295 was a 12-week double-blind placebo-controlled study, in which CM subjects were randomized in a 3:2:2 ratio to placebo, erenumab 70 mg, or 140 mg. There was a statistically significant greater mean reduction in the change in MMD from baseline to the last 4 weeks of the 12-week DBTP for AMG 334 70 mg and 140 mg compared with placebo. The difference in LSM (95% CI) versus placebo was -2.46 (-3.52, -1.39) days and -2.45 (-3.52, -1.38) days for erenumab 70 mg and 140 mg, respectively ( $p < 0.001$  for both doses). The proportion of subjects with at least a 50% reduction in MMD from baseline to the last 4 weeks of the DBTP was 23.5%, 39.9%, and 41.2% for the placebo, erenumab 70 mg, and erenumab 140 mg groups, respectively; results were statistically significant for each erenumab group versus placebo ( $p < 0.001$  for both doses). Furthermore, for the endpoint of change in monthly acute migraine-specific medication treatment days from baseline to the last 4 weeks of the DBTP, the difference in LSM (95% CI) versus placebo was -1.86 (-2.60, -1.13) days and -2.55 (-3.28, -1.82) days for erenumab 70 mg and 140 mg, respectively ( $p < 0.001$  for both doses).

The overall percentage of subjects with a treatment-emergent adverse event was 39.0%, 43.7%, and 46.8% for the placebo, erenumab 70 mg, and erenumab 140 mg groups, respectively. The overall percentage of subjects with a serious adverse event was 2.5%, 3.2%, and 1.1% for the placebo, erenumab 70 mg, and erenumab 140 mg groups, respectively. Two subjects (0.7%) in the placebo group, 0 subjects in the erenumab 70 mg group, and 2 subjects (1.1%) in the erenumab 140 mg group had adverse events leading to withdrawal of investigational product. No fatal treatment-emergent adverse events were reported. The most common events ( $\geq 2\%$  of subjects in all erenumab subjects combined) are listed in [Table 5-2](#).

**Table 5-2. Treatment-emergent Adverse Events Occurring in  $\geq 2\%$  of Subjects in the All Erenumab Group, Preferred Term (Safety Analysis Set)**

Preferred Term	Placebo (N = 282) n (%)	Erenumab		
		70 mg (N = 190) n (%)	140 mg (N = 188) n (%)	All erenumab (N = 378) n (%)
Number of subjects reporting treatment-emergent adverse events	110 (39.0)	83 (43.7)	88 (46.8)	171 (45.2)
Injection site pain	3 (1.1)	7 (3.7)	7 (3.7)	14 (3.7)
Upper respiratory tract infection	4 (1.4)	5 (2.6)	6 (3.2)	11 (2.9)
Nausea	7 (2.5)	4 (2.1)	6 (3.2)	10 (2.6)
Nasopharyngitis	16 (5.7)	6 (3.2)	3 (1.6)	9 (2.4)
Constipation	1 (0.4)	0 (0.0)	8 (4.3)	8 (2.1)
Muscle spasms	4 (1.4)	1 (0.5)	7 (3.7)	8 (2.1)
Migraine	3 (1.1)	3 (1.6)	5 (2.7)	8 (2.1)

N = number of subjects in the analysis set; n = number of subjects reporting at least one occurrence of an adverse event in that class; % =  $n/N \times 100$ .

Coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.0.

Source: Study 20120295 Final Analysis CSR.

The frequencies of adverse events, serious adverse events, and adverse events leading to discontinuation of investigational product were similar across the placebo, erenumab 70 mg, and erenumab 140 mg groups.

The dose of 70 mg erenumab in this study is supported by: comparable efficacy observed between 70 mg and 140 mg in Study 20120295; results from Study 20120309 demonstrating maximal efficacy for 70 mg with no incremental efficacy for 140 mg in the primary and secondary endpoints; and similar safety profiles of the 70 mg and 140 mg doses in Study 20120295 and Study 20120309.

## 5.5 Patient Input on Study Design

Patient input was not collected during the study design.

## 5.6 Definitions of Terms Included in Endpoints

Migraine Day: Any calendar day in which the subject experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura, lasting for  $\geq 4$  hours, and meeting at least 1 of the following criteria:

1.  $\geq 2$  of the following pain features:

- unilateral
- throbbing

- moderate to severe
  - exacerbated with exercise/physical activity
2.  $\geq 1$  of the following associated symptoms:
- nausea
  - vomiting
  - photophobia and phonophobia

If the subject took a migraine-specific medication (ie, triptan or ergotamine) during aura or to treat headache on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms.

**Headache Day:** Any calendar day in which the subject experiences a qualified headache (initial onset, continuation or recurrence of the headache). A qualified headache is defined as:

- a qualified migraine headache (including an aura-only event that is treated with acute migraine-specific medication)
- or a qualified non-migraine headache, which is a headache that lasts  $\geq 4$  hours and is not a qualified migraine headache
- or a headache of any duration for which acute headache treatment is administered

**Acute Headache Medication Treatment Day:** Any calendar day during which the subject took an acute headache medication (migraine-specific or not migraine-specific).

**Acute Migraine-specific Medication Treatment Day:** Any calendar day during which the subject took a migraine-specific medication (ie, triptan or ergotamine).

**Monthly Electronic Diary (eDiary) Data:** Data collected by the eDiary in any 28-consecutive day interval relative to study day 1 when at least 14 days of eDiary data are collected within that 28-consecutive day interval. Monthly frequency measurements will be prorated to 28-day equivalents.

## **6. Study Population**

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log may be completed and updated via an Interactive **Response Technology** (IRT).

Part 1 eligibility criteria will be evaluated during screening. At the end of screening period, subjects who successfully met eligibility criteria will undergo a 4-week baseline period. At the end of Part 2, eligibility requirements will then be assessed.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see [Section 12.3](#)).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, will not be provided.

## **6.1 Inclusion Criteria Part 1**

These inclusion criteria are to be assessed during the screening period prior to enrollment into the baseline period:

- 101 Subject has provided informed consent/assent prior to initiation of any study specific activities/procedures.
- 102 Japanese subjects  $\geq 20$  to  $\leq 65$  years of age upon entry into screening.
- 103 History of migraine (with or without aura) for  $\geq 12$  months before screening according to the International Headache Society Classification ICHD-3 ([Headache Classification Committee of the International Headache Society, 2018](#)) based on medical records and/or patient self-report.
- 104 Migraine frequency: CM or EM over the 3 months before screening (refer to [Section 5.6](#) for definition of migraine day) based on the following criteria:
  - (a) CM is defined as  $\geq 15$  headache days per month of which  $\geq 8$  headache days meet criteria as migraine days on average across the 3 months.
  - (b) EM is defined as  $< 15$  headache days per month of which  $\geq 4$  headache days meet criteria as migraine days on average across the 3 months.

## **6.2 Exclusion Criteria Part 1**

Subjects are excluded from the study if any of the following criteria apply:

### **Disease Related**

- 201 Subjects  $> 50$  years of age at migraine onset.
- 202 History of cluster headache or hemiplegic migraine headache.
- 203 Unable to differentiate migraine from other headaches.
- 204 Migraine with continuous pain, in which the subject does not experience any pain-free periods (of any duration) during the 1 month before the screening period.

### **Other Medical Conditions**

- 205 Malignancy, except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ within the last 5 years.
- 206 History of major psychiatric disorder (such as schizophrenia and bipolar disorder), or current evidence of depression based on a Beck Depression Inventory (BDI)-2 total score  $> 19$  at screening. Subjects with anxiety disorder and/or major depressive disorder are permitted in the study if they are considered by the investigator to be stable (with BDI-2  $\leq 19$ ) and are taking no more than 1 medication for each disorder. Subjects must have been on a stable dose within the 3 months prior to the start of the baseline period.

- 207 History of seizure disorder or other significant neurological conditions other than migraine. Note: A single childhood febrile seizure is not exclusionary.
- 208 The subject is at risk of self-harm or harm to others as evidenced by past suicidal behavior or endorsing items 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) assessed at screening.
- 209 Active chronic pain syndromes (such as fibromyalgia and chronic pelvic pain).
- 210 Known human immunodeficiency virus infection.
- 211 Known hepatic disease with potential for hepatic function impairment or known history of acute or chronic hepatitis B or hepatitis C.
- 212 Diagnosis of Gilbert's Syndrome.
- 213 Evidence of drug or alcohol abuse or dependence or "recreational use" of illicit drugs within 12 months prior to screening, based on medical records, patient self-report, or positive urine drug test performed during screening (with the exception of prescribed medications such as opioids or barbiturates).
- 214 Myocardial infarction, stroke, TIA, unstable angina, coronary artery bypass surgery, or other revascularization procedure within 12 months prior to screening.

#### **Prior/Concomitant Therapy**

- 215 No therapeutic response with > 3 of the following 8 medication categories for preventive treatment of migraine after an adequate therapeutic trial:
  - Category 1: divalproex sodium, sodium valproate.
  - Category 2: topiramate.
  - Category 3: beta blockers (eg, atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol).
  - Category 4: tricyclic antidepressants (eg, amitriptyline, nortriptyline, protriptyline).
  - Category 5: serotonin-norepinephrine reuptake inhibitors (eg, venlafaxine, desvenlafaxine, duloxetine, milnacipran).
  - Category 6: flunarizine, verapamil, lomerizine.
  - Category 7: lisinopril, candesartan.
  - Category 8: botulinum toxin.

No therapeutic response is defined as no reduction in headache frequency, duration, or severity after administration of the medication for at least 6 weeks at the generally-accepted therapeutic dose(s) and is based on the investigator's assessment.

The following scenarios do not constitute lack of therapeutic response:

- Lack of sustained response to a medication.
- Failure to tolerate a therapeutic dose.

- 216 Concomitant use of 2 or more medications with possible migraine preventive effects within 2 months prior to the start of the baseline period.
- If only 1 preventive medication is used, the dose must be stable within 2 months prior to the start of the baseline period and throughout the study.
- 217 Used a prohibited medication, device, or procedure within 2 months prior to the start of the baseline period (refer to [Section 7.1.7](#) for the list of excluded medications, devices, and procedures).
- 218 Received botulinum toxin in the head and/or neck region within 4 months prior to the start of the baseline period.
- 219 Taken an opioid- or butalbital-containing analgesic on  $\geq 4$  days per month for any indication in any month during the 2 months prior to the start of the baseline period.
- 220 Current use or any prior use of a CGRP monoclonal antibody.**
- 221 Anticipated to require any excluded medication/device (eg, nerve stimulators, transcranial magnetic stimulation) or procedure during the study (Refer to [Section 7.1.7](#) for the list of excluded medications, devices, and procedures).

#### **Prior/Concurrent Clinical Study Experience**

- 222 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

#### **Diagnostic Assessments**

- 223 Total bilirubin  $\geq 2.0 \times$  upper limit of normal (ULN) or alanine aminotransferase (ALT) or aspartate aminotransferase (AST)  $\geq 3.0 \times$  ULN, as assessed by the central laboratory at screening.
- 224 Subject has any clinically significant vital sign, laboratory, or electrocardiogram (ECG) abnormality during screening that, in the opinion of the investigator, could pose a risk to subject safety or interfere with the study evaluation.

#### **Other Exclusions**

- 225 Body mass index (BMI)  $> 40 \text{ kg/m}^2$  as assessed at screening.
- 226 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 12 weeks after the last dose of investigational product.
- 227 Female subjects of childbearing potential unwilling to use 1 acceptable method of effective contraception during treatment and for an additional 12 weeks after the last dose of investigational product. Refer to [Section 12.5](#) for additional contraceptive information.
- 228 Female subjects of childbearing potential with a positive pregnancy test assessed at screening by a serum pregnancy.
- 229 Subject has known sensitivity to any of the products or components to be administered during dosing.



- 230 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, clinical outcome assessments [COAs]) to the best of the subject and investigator's knowledge.
- 231 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.
- 232 Previously randomized into an erenumab study or treated with erenumab.
- 233 Investigational site staff or relatives of the investigator.

### **6.3 Inclusion Criteria Part 2**

Criteria to be assessed prospectively during the 4-week baseline period and confirmed before randomizing the subject into the DBTP:

- 105 Must meet 1 of the following migraine criteria and must also be the same migraine type in [Inclusion Criterion 104](#) of Part 1 (for example, if a subject meets EM criteria in the previous 3 months before screening, then the subject must meet EM criteria during baseline):
  - (a) CM is defined as  $\geq 15$  headache days of which  $\geq 8$  headache days meet criteria as migraine days during the baseline period based on the eDiary calculations.
  - (b) EM is defined as  $< 15$  headache days of which  $\geq 4$  headache days meet criteria as migraine days during the baseline period based on the eDiary calculations.
- 106 Demonstrated at least 80% compliance with the eDiary during the baseline period.

### **6.4 Exclusion Criteria Part 2**

Subjects are excluded from the study if any of the following criteria apply:

#### **Concomitant treatment at baseline**

- 234 Taken an opioid- or butalbital-containing analgesic on  $\geq 4$  days per month for any indication during the baseline period.
- 235 Concomitant use of 2 or more medications with possible migraine preventive effects during the baseline period. If only 1 preventive medication is used, the dose must be stable during the baseline period and throughout the study.
- 236 Received botulinum toxin in the head and/or neck region during the baseline period.
- 237 Current use or any prior use of a CGRP monoclonal antibody.**
- 238 Used a prohibited medication, device or procedure during the baseline period (refer to [Section 7.1.7](#) for the list of these excluded treatments and the timeframes).

### **Medical conditions newly diagnosed during baseline**

- 239 The subject is at risk of self-harm or harm to others as evidenced by past suicidal behavior or endorsing items 4 or 5 on the C-SSRS assessed at baseline.
- 240 Unstable or clinically significant medical condition that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.
- 241 Subject has any clinically significant vital sign, laboratory, or ECG abnormality during baseline that, in the opinion of the investigator, could pose a risk to subject safety or interfere with the study evaluation.

### **Contraception, pregnancy or breastfeeding**

- 242 Unwillingness to maintain acceptable contraception method, when applicable (refer to [Criterion, 226, 227, and 228](#)).
- 243 Evidence of pregnancy or breastfeeding per subject self-report, medical records or positivity on baseline pregnancy screening tests.

## **6.5 Subject Enrollment**

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see [Section 12.3](#)).

The subject or the subject's legally acceptable representative must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

A subject may proceed to the baseline period when the investigator decides that the subject has met all Part 1 eligibility criteria..

Upon completion of baseline period procedures, the subject is evaluated by the investigator, and if the subject meets all Part 2 eligibility criteria he/she is subsequently enrolled and randomized to a treatment regimen. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF). Subjects who do not meet Part 2 eligibility criteria will be screen-failed.

Each subject who enters into the screening period for the study (defined as when the subject signs and dates the informed consent form) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned via **IRT**. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment. This number will not be the same as the randomization number assigned for the study.

## **6.6 Screen Failures**

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

## **7. Treatments**

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in [Table 7-1](#) below.

### **7.1 Treatment Procedures**

#### **7.1.1 Investigational Products**

Approved

**Table 7-1. Study Treatments**

Amgen Investigational Product: <sup>a</sup>		
Study Treatment Name	Erenumab	Placebo
<b>Dosage Formulation</b>	Erenumab will be packaged in 1 mL prefilled syringes containing 70 mg/mL erenumab formulated with sodium acetate, sucrose, polysorbate 80, at pH 5.2.	Placebo consisting of sodium acetate, sucrose, polysorbate 20, at pH 5.2 will be packaged to match the active drug product.
<b>Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency</b>	70 mg monthly	N/A
<b>Route of Administration</b>	Subcutaneously (SC) injection only	
<b>Accountability</b>	The quantity, start date/time, injection site, and box number of investigational product are to be recorded on each subject's case report form (CRF).	
<b>Dosing Instructions</b>	<ul style="list-style-type: none"> <li>Double-blind erenumab 70 mg, will be administered during the 24-week double-blind treatment period (ie, at day 1 and weeks 4, 8, 12, 16, and 20) and erenumab 70 mg will be administered during the 28-week open-label treatment period (ie, at weeks 24, 28, 32, 36, 40, 44, and 48).</li> <li>Only authorized investigational site study staff members are to administer Amgen investigational product.</li> <li>Investigational product doses are fixed and will not be adjusted for individual subjects during the study.</li> <li>The anatomical sites for administration of investigational product are the upper arm, upper thigh, or abdomen.</li> <li>Overdose with this product has not been reported.</li> </ul>	
<b>Device</b>	Prefilled syringe	

<sup>a</sup> Erenumab will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

Approved

### **7.1.2 Non-investigational Products**

Non-investigational products will not be used in this study.

### **7.1.3 Medical Devices**

The following investigational medical device(s) provided by Amgen for use in this study is the prefilled syringe ([Table 7-1](#)).

The erenumab prefilled syringe is a single-use, disposable, handheld manual injection device for fixed dose subcutaneous injection of 70 mg in a 1 mL deliverable volume.

Additional details are provided in the IPIM.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

### **7.1.4 Other Protocol-required Therapies**

There are no other protocol-required therapies for this study.

### **7.1.5 Other Treatment Procedures**

There are no other treatment procedures for this study.

### **7.1.6 Product Complaints**

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any investigational product(s) or device(s) provisioned and/or repackaged/modified by Amgen.

Any product complaint(s) associated with an investigational product(s) or devices(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

### **7.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period**

1. More than 1 of the following medications with possible migraine preventive effects are excluded within 2 months prior the start of the baseline period and throughout the study. If 1 of the following medications is used, doses must be stable within 2 months prior to the start of the baseline period and throughout the study:
  - divalproex sodium, sodium valproate, topiramate, carbamazepine, gabapentin
  - beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)
  - tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline)
  - venlafaxine, desvenlafaxine, duloxetine, milnacipran
  - flunarizine, verapamil, lomerizine
  - lisinopril, candesartan
  - clonidine, guanfacine
  - cyproheptadine
  - methysergide
  - pizotifen
  - butterbur, feverfew, magnesium ( $\geq 600$  mg/day), riboflavin ( $\geq 100$  mg/day)
2. The following medications are excluded only if used daily throughout the month for migraine prevention:
  - fluoxetine, fluvoxamine
  - acetazolamide
  - picotamide
  - cyclandelate
  - ergot-derivatives, steroids, triptans
  - nocardipine, nifedipine, nimodipine

If the above medications are used daily for migraine prevention, subjects must have been free from these medications for at least 2 months prior to the start of the baseline period.

3. Botulinum toxin (in the head and/or neck region) is excluded within 4 months prior to the start of the baseline period and throughout the study.
4. An anti-CGRP monoclonal antibody is excluded throughout the study. Current use and any prior use is excluded.
5. Devices and procedures used for migraine prevention are excluded within 2 months prior to the start of the baseline period and throughout the study.
6. Investigational medications and devices, and procedures are excluded throughout the study. Subjects also must not have used investigational medications, devices or procedures for at least 30 days prior to screening (refer to [Exclusion Criterion 221](#)).

## **7.2 Method of Treatment Assignment**

Subjects will be randomized in 1:1 allocation ratio to erenumab or placebo, respectively, in double-blind manner with approximately 128 subjects randomized to placebo and approximately 128 subjects randomized to erenumab 70 mg (in each arm, approximately 78 subjects with EM and 50 subjects with CM).

The randomization will be performed by **IRT** and the randomization number will be assigned by **IRT**.

The subjects will be stratified by EM/CM and migraine preventive treatment status (ever used [prior and/or current] or never used). There may be a limit on the percentage of subjects with current use of a migraine preventive treatment.

The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

## **7.3 Blinding**

This is a double-blind study only during the DBTP. Treatment assignment will be blinded to all subjects, site personnel, and Amgen as described below.

### **7.3.1 Site Personnel Access to Individual Treatment Assignments**

A subject's treatment assignment is to only be unblinded by the investigator when knowledge of the treatment is essential for the further management of the subject on this study or may potentially impact the safety of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation. It is encouraged that the Amgen Trial Manager be notified before the blind is broken unless the investigator believes that identification of the study treatment is required for a medical emergency. If this is not possible, the Amgen Trial Manager must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.

### **7.3.2 Access to Individual Subject Treatment Assignments by Amgen or Designees**

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information is not to be distributed to the study team, investigators, or subjects prior to the study being formally unblinded at the primary analysis.

## **7.4 Dose Modification**

### **7.4.1 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation**

Amgen Investigational Product: erenumab

The dosage of investigational product is fixed for all subjects and cannot be adjusted.

Missed or delayed doses should be noted on the investigational product administration CRF, but no attempt should be made to administer any missed doses at the subject's next visit.

At any time during the study, the investigator may discontinue investigational product administration for any subject who experiences a severe or life-threatening adverse event reported by the investigator to be related to investigational product. Refer to [Section 9.2.3.1](#) for details regarding adverse event reporting.

Subjects who permanently discontinue investigational product during the DBTP are to continue to return for all other study procedures until the end of the DBTP and study procedures for the safety follow-up visit 12 weeks after the last dose of investigational product.

Subjects who permanently discontinue investigational product during the OLTP are to complete the study procedures for the week 52/ET visit and the safety follow-up visit 12 weeks after the last dose of investigational product.

End of investigational product and early discontinuation from investigational product are to be registered in the IRT System.

### **7.4.2 Hepatotoxicity Stopping and Rechallenge Rules**

Refer to [Section 12.7](#) for details regarding drug-induced liver injury guidelines, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

## **7.5 Preparation/Handling/Storage/Accountability**

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product and device during the study are provided in the IPIM.

## **7.6 Treatment Compliance**

Administration of investigational product will be conducted at sites during scheduled visits.



Noncompliance is to be documented in the medical file and will be reflected in the electronic CRF. Noncompliant subjects are to be re-educated on the importance of adhering to the investigational product administration schedule and reminded that repeated cycles of noncompliance could be a reason for discontinuation of study treatment.

## **7.7 Treatment of Overdose**

Overdose with this product has not been reported.

## **7.8 Prior and Concomitant Treatment**

### **7.8.1 Prior Treatment**

Prior therapies that were being taken/used from 120 days before screening through the signing of the informed consent will be collected.

### **7.8.2 Concomitant Treatment**

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in [Section 7.1.7](#).

Concomitant therapies are to be collected from the signing of the informed consent through the end of safety follow-up period (12 weeks after the last dose of investigational product).

The subject may take 1 medication with possible migraine preventive effects. These medications (listed in [Section 7.1.7](#)) should not change for the duration of the study and the doses should be stable for 2 months prior to the start of the baseline period and throughout the study.

During the initial screening period, the subject and investigator are to agree on the acute headache medications and the appropriate dose(s) that the subject may take on an as-needed basis throughout the study. To avoid confounding the study results, efforts should be made throughout the study to not introduce new acute migraine-specific medications (ie, triptans or ergotamines).

## **8. Discontinuation Criteria**

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in

[Sections 8.1 and 8.2.](#)

### **8.1 Discontinuation of Study Treatment**

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see [Table 2-1](#)) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with [Section 12.3.](#)

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- decision by sponsor
- lost to follow-up
- death
- ineligibility determined
- protocol deviation
- non-compliance
- adverse event
- subject request
- pregnancy

## **8.2 Discontinuation From the Study**

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see [Section 12.6](#) for further details). Refer to the Schedule of Activities ([Table 2-1](#)) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

**8.2.1 Reasons for Removal From Washout, Run-in or Invasive Procedures**  
Not applicable.

**8.2.2 Reasons for Removal From Study**  
Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

## **8.3 Lost to Follow-up**

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.

- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator can search publicly available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

## **9. Study Assessments and Procedures**

Study procedures and their timepoints are summarized in the Schedule of Activities (see [Table 2-1](#)).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

### **9.1 General Study Periods**

#### **9.1.1 Screening, Enrollment and/or Randomization**

##### **9.1.1.1 Screening Period and Baseline Period**

##### **9.1.1.1.1 Screening Period**

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will register the subject in the **IRT** and screen the subject in order to assess eligibility for participation. The screening period is up to 7 weeks, which consists of an initial screening period of up to 3 weeks and a baseline period of 4 weeks.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

If a subject has not met all Part 1 eligibility criteria at the end of the screening period, the subject will be registered as a screen fail.

##### **9.1.1.1.2 Baseline Period**

The 4-week baseline period starts when the subject has met all Part 1 eligibility criteria (refer to [Section 6.1](#) and [Section 6.2](#)) and is entered in the baseline period and ends either with screen failure or is randomized.

#### **9.1.1.2 Randomization**

On completion of the baseline period, subjects found to meet eligibility requirements will undergo randomization and will be assigned a study treatment.

#### **9.1.2 Treatment Period**

Visits will occur per the Schedule of Activities ([Table 2-1](#)). On-study visits may be completed within 3 days. The date of the first dose of protocol-required therapies is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of protocol-required therapies is to be administered last during each visit that it is required.

#### **9.1.3 Early Termination**

Upon permanent discontinuation from the study treatment for any reason, an ET visit will be performed approximately 30 (+3) days after the last dose of investigational product.

Subjects who early terminate the study treatment before or at week 24 should complete the week 24/ET assessments ([Table 2-1](#)).

Subjects who early terminate the study treatment after week 24 and before week 52 should complete the week 52/ET assessments ([Table 2-2](#)).

#### **9.1.4 Safety Follow-up**

A safety follow-up visit will be performed 12 weeks after the last dose of investigational product, which can occur during the DBTP or OLTP ([Table 2-1](#) or [Table 2-2](#)).

#### **9.1.5 End of Study**

Subjects who complete safety follow-up will end the study and complete all EOS assessments according to [Table 2-1](#) or [Table 2-2](#).

### **9.2 Description of General Study Assessments and Procedures**

The sections below provide a description of the individual study procedures for required timepoints.

#### **9.2.1 General Assessments**

##### **9.2.1.1 Informed Consent**

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

#### **9.2.1.2 Calls to Interactive Response Technology (IRT) System**

Sites are to call the **IRT** system for the following: to enter the subject into the initial screening period, to randomize an eligible subject, to obtain the investigational product assignment, to enter the subject into the OLTP, to register the end of investigational product, and to register study ET or completion. Subject data will be collected in the **IRT** system including, but not limited to reason for screen fail (if applicable).

#### **9.2.1.3 Demographics**

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on biomarkers, variability, and pharmacokinetics (PKs) of the protocol-required therapies.

#### **9.2.1.4 Medical History**

The Investigator or designee will collect a complete medical, psychiatric, and surgical history that started within 120 days prior to enrollment through day 1. A lifetime cardiovascular history will also be collected. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. In addition to the medical history above, migraine history must date back to the original diagnosis. The current severity will be collected for each condition that has not resolved.

#### **9.2.1.5 Physical Examination**

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

#### **9.2.1.6 Physical Measurements**

Height in centimeters should be measured without shoes. Weight in kilograms should be measured without shoes.

All measurements are to be recorded on the Physical Measurements CRF.

Approved

#### **9.2.1.7 Hepatitis Testing**

- If a hepatic event is suspected during the study, hepatitis testing will be performed on a blood sample collected and stored during screening and a blood sample collected during the event. Hepatitis testing will be performed by the central laboratory. The following laboratory testing will be performed:
  - Hepatitis B Surface Antigen (HepBsAg) and total Hepatitis B Core Antibody (HepBcAb)
  - Hepatitis B Virus DNA Real-time polymerase chain reaction (PCR) will be only performed if total HepBcAb is positive and HepBsAg is negative
  - Hepatitis C virus antibody
  - Hepatitis C Virus RNA Real-time PCR will be only performed if hepatitis C virus antibody is positive

#### **9.2.1.8 Urine Drug Screening**

Subjects will be tested for substances of abuse at initial screening to confirm subject eligibility. During the study, urine drug tests can also be performed at the investigator's discretion based on clinical suspicion. Urine samples will be analyzed by the central laboratory. For a subject with a positive urine drug screen during the study (except for certain prescribed medications), the investigator should consider discontinuing the subject from investigational product.

### **9.2.2 Efficacy Assessments**

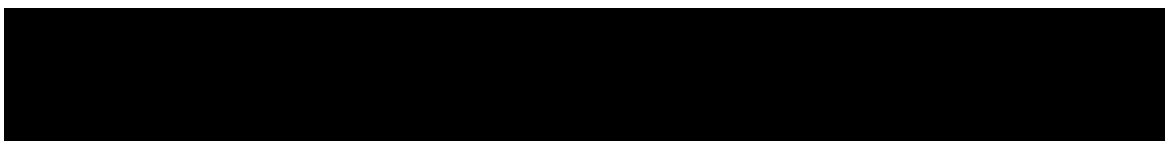
#### **9.2.2.1 Clinical Outcome Assessments**

Clinical Outcome Assessments will be collected by subjects using a handheld eDiary at various frequencies.

The eDiary will collect the following COAs daily at home in the DBTP and daily during weeks 33 to 36 and weeks 49 to 52 in the OLTP:

- date and time of start of headache (ie, migraine or non-migraine headache)
- date and time of end of headache
- worst pain severity per headache
- pain features (eg, 1-sided, throbbing, worsens with exercise/physical activity)
- symptoms (eg, aura, nausea, vomiting, photophobia, phonophobia)
- use of acute headache medications (medication name [from pre-entered list], date of dosing, number of times taken on each date)

The eDiary will collect the following PROs:

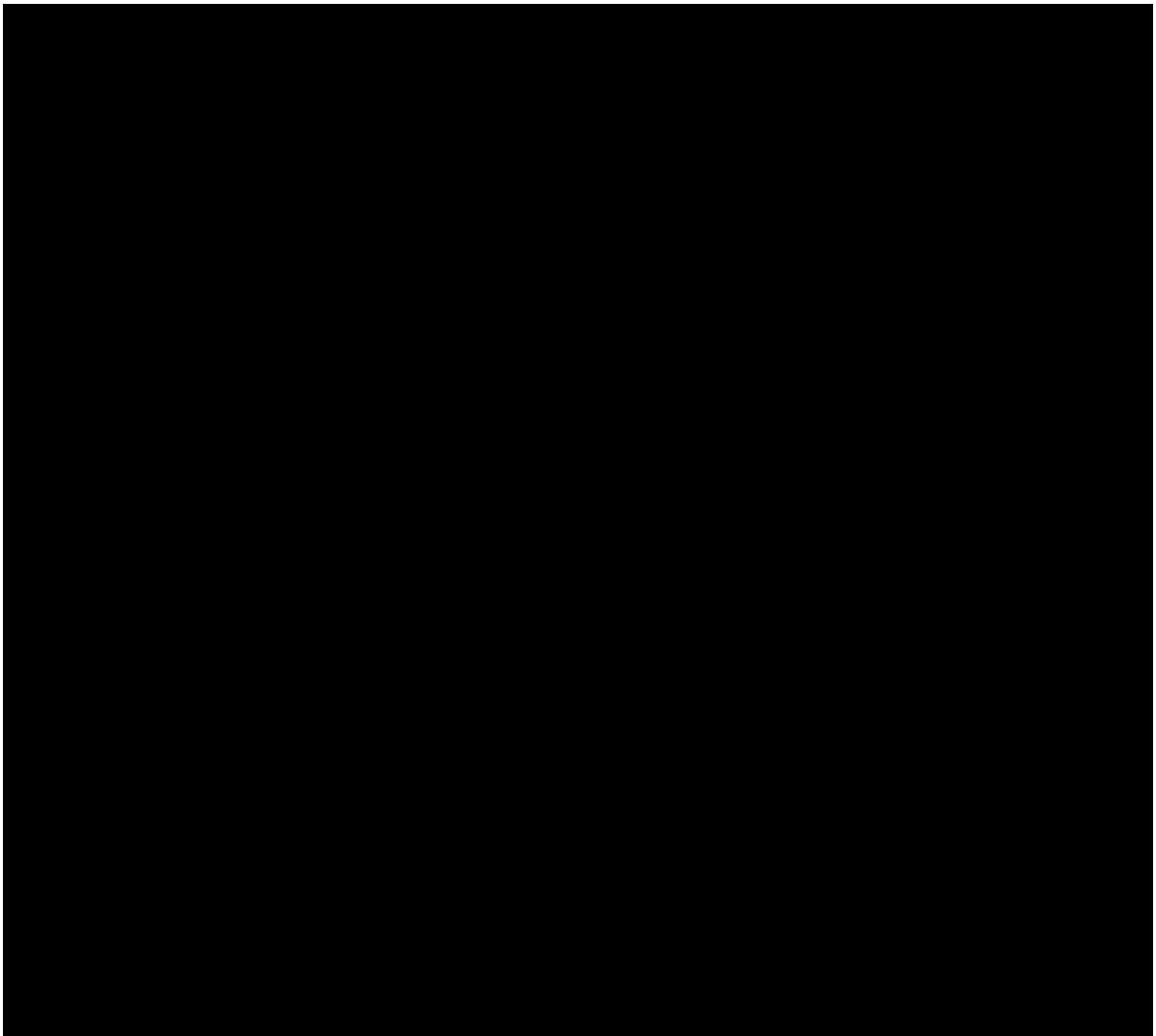




- BDI-2, in clinic at day 1 and week 24/ET in the DBTP

Site study staff will assign and provide an eDiary to the subject at the week -4 visit (after confirming the subject's eligibility to enter the baseline period). The site study staff will train the subject on how to use the eDiary (eg, turning on/off, charging, navigating screens, transmitting data, contacting the help desk for technical assistance) and complete the questions. The subject will be instructed to interact with the eDiary every day and to bring the eDiary to every study visit. At the day 1 study visit the investigator will use the subject's eDiary to review all data entered during the baseline period and confirm the relevant inclusion and exclusion criteria.

Please refer to the eDiary manual for additional details.



Approved



Approved

#### **9.2.2.6 Beck Depression Inventory**

The BDI-2 is a 21-item questionnaire that assesses severity of depression. Each item is scored from 0 to 3. The total score is categorized into 4 severity grades: minimal depression (0 - 13), mild depression (14 - 19), moderate depression (20 - 28), and severe depression (29 - 63).

#### **9.2.3 Safety Assessments**

Planned timepoints for all safety assessments are listed in the Schedule of Activities (see [Table 2-1](#) and [Table 2-2](#)).

### **9.2.3.1 Adverse Events**

#### **9.2.3.1.1 Time Period and Frequency for Collecting and Reporting Safety Event Information**

##### **9.2.3.1.1.1 Adverse Events**

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) and is described in [Section 12.4](#).

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product through the safety follow-up visit or end of study, whichever is later, are reported using the Event CRF.

##### **9.2.3.1.1.2 Serious Adverse Events**

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the safety follow-up visit or end of study, whichever is later, are reported using the Event CRF.

All serious adverse events will be collected, recorded, and reported to the sponsor or designee within 24 hours, as indicated in [Section 12.4](#). The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

##### **9.2.3.1.1.3 Serious Adverse Events After the Protocol-required Reporting Period**

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. Per local requirements in some countries, investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in [Section 12.4](#).

#### **9.2.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events**

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

#### **9.2.3.1.3 Follow-up of Adverse Events and Serious Adverse Events**

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in [Section 8.3](#)).

Further information on follow-up procedures is given in [Section 12.4](#).

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

#### **9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events**

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team as appropriate. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

#### **9.2.3.1.5 Pregnancy and Lactation**

Details of all pregnancies and/or lactation in female subjects and, if indicated, female partners of male subjects will be collected after the start of study treatment and until 12 weeks after last dose of investigational product.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in [Section 12.5](#). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in [Section 12.5](#).

#### **9.2.3.1.6 Adverse Device Effects**

In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of any adverse device effects that occur during the study with such devices.

An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

All adverse device effects are to be reported as adverse events following the same reporting periods and procedures.

Product complaints are described in [Section 7.1.6](#).

Further details regarding adverse device effects can be found in [Section 12.4](#).

#### **9.2.3.2 Vital Signs**

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the Vital Signs CRF.

Blood pressure will be measured in the following manner:

- Subjects should be lying in a semi-recumbent position (partial semi-Fowler's position) or supine position quietly and comfortably for at least 5 minutes. The upper arm should be bare without constrictive clothing and supported at heart level.
- Caffeine, exercise, and smoking should be avoided for at least 30 minutes prior to measurement.
- An appropriately-sized cuff (cuff bladder encircling at least 80 percent of the arm) should be used to ensure accuracy. At least 2 measurements (separated by at least 5 minutes) should be made and the average recorded. If there is a high value, it is acceptable to wait approximately 30 minutes before the next 2 blood pressure measurements are taken for the purpose of averaging and recording in the CRF.
- Blood pressure will initially be recorded in both of the subject's arms unless a concomitant condition favors the use of a particular arm. The arm with the higher systolic reading at initial screening should then be used for blood pressure determinations throughout the study.
- Neither the subject nor the observer (measurer) should talk during measurement.

If abnormalities are found and they are considered to be an adverse event, record on the Adverse Event CRF.

#### **9.2.3.3 Electrocardiograms**

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The ECG must include the following measurements: heart rate, QRS, QT, QTc, and PR intervals. The **principal** investigator or designated site physician will review all ECGs. Once signed,

the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

It is the responsibility of the investigator to determine if the ECG tracings are consistent with a subject's safe participation in the study.

#### **9.2.3.4 Suicidal Risk Monitoring**

##### **9.2.3.4.1 Columbia-suicide Severity Rating Scale (C-SSRS)**

The C-SSRS is a clinician rating of suicidal behavior and ideation. The C-SSRS consists of a maximum of 20 items, which defines 5 subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent. The C-SSRS will be administered by the principal investigator or qualified designee. Reports of suicidal ideation with intent to act (severity of 4 or 5) and reports of actual, aborted, or interrupted suicide attempts or a behavior preparatory for making an attempt indicate subjects at high risk for suicide. If such reports are identified at screening, this is considered an exclusion criteria. If such reports are identified on-study, the investigator is to appropriately manage the subject in accordance with standard of care.

##### **9.2.3.5 Other Safety**

Not applicable.

#### **9.2.4 Clinical Laboratory Assessments**

Refer to [Section 12.2](#) for the list of clinical laboratory tests to be performed and to the Schedule of Activities ([Table 2-1](#)) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in [Section 12.2](#), must be conducted in accordance with the laboratory manual and the Schedule of Activities ([Table 2-1](#)).

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

#### **9.2.4.1 Pregnancy Testing**

A high sensitive serum pregnancy test should be completed at screening and at the safety follow-up visit for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Worksheet, see [Figure 12-2](#)). Refer to [Section 12.5](#) for contraceptive requirements.

Additional urine pregnancy testing should be performed at monthly intervals during treatment with protocol-required therapies and up to 12 weeks after the last dose of protocol-required therapies.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

#### **9.2.4.2 Prespecified Biomarker Assessments**

Not applicable.

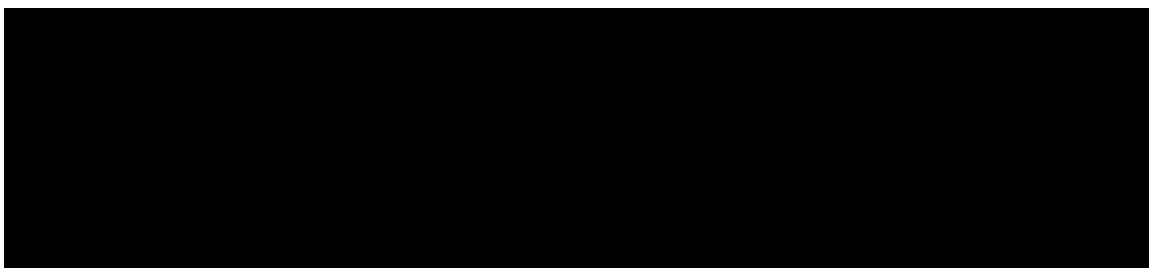
#### **9.2.5 Pharmacokinetic Assessments**

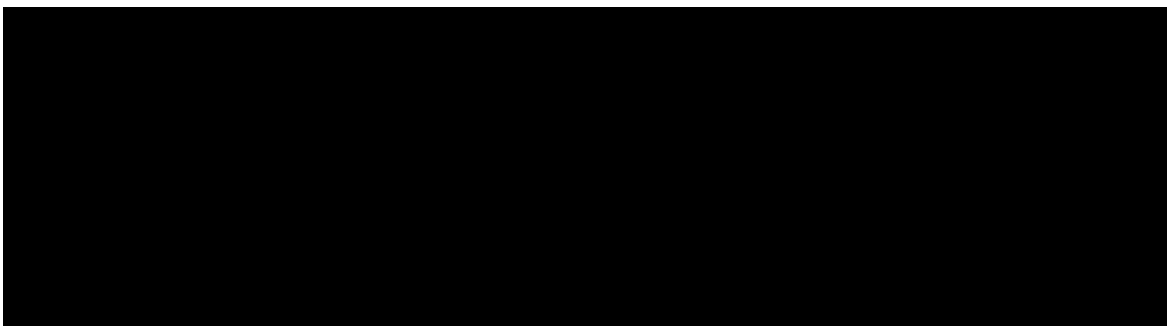
All subjects who meet the Part 2 eligibility criteria will have PK samples assessed at day 1 for baseline purposes.

Blood samples of approximately **29.5** mL will be collected for measurement of blood concentrations of erenumab as specified in the Schedule of Activities ([Table 2-1](#) and [Table 2-2](#)).

Please refer to the central laboratory manual for instructions on sample collection, processing, and shipping of PK samples. The actual date and time (24-hour clock time) of each sample will be recorded.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.





### 9.2.7 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected according to the timepoints specified in the Schedule of Activities ([Table 2-1](#)) for the measurement of anti-erenumab binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. Additional blood samples may be obtained to rule out anti-erenumab antibodies during the study.

Sites will be notified of any positive neutralizing antibody results to erenumab for individual subjects at the end of the study for each subject. If results are not provided, no neutralizing antibodies to erenumab have been detected.

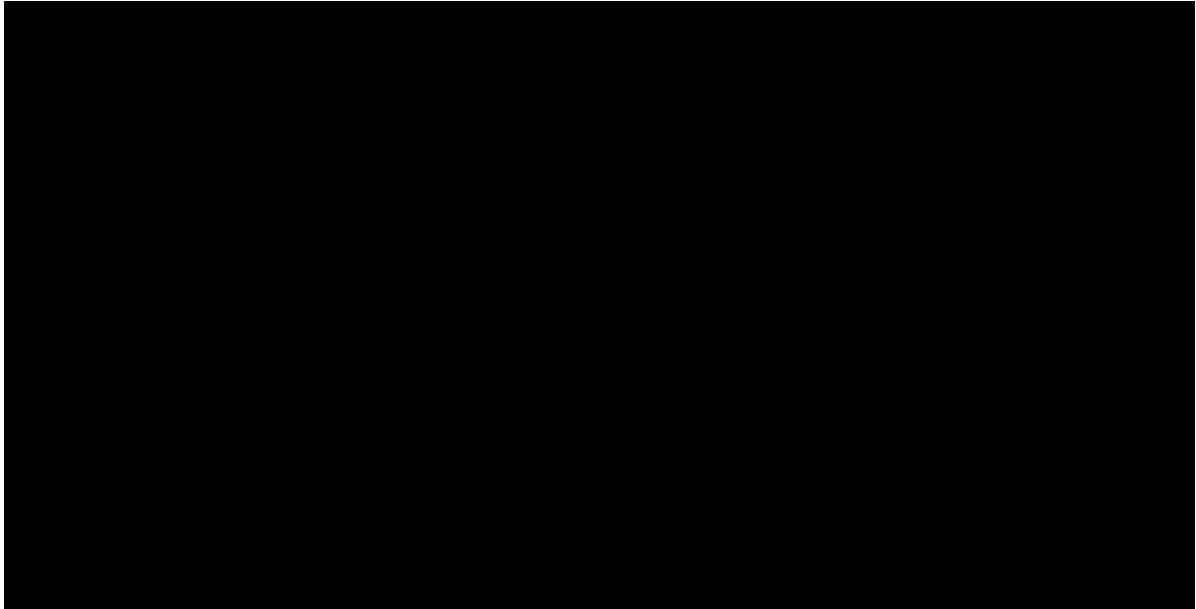
This notification is independent of and may be in advance of the time point when the entire study is planned to be unblinded. Refer to [Section 7.3](#) for additional information regarding unblinding.

Subjects who test positive for neutralizing antibodies to erenumab at the final scheduled study visit defined as the end of treatment visit will be asked to return for additional follow-up testing. This testing is to occur approximately every 3 months starting from when the site has been notified of the positive result until: (1) neutralizing antibodies are no longer detectable; or (2) the subject has been followed for a period of at least 1 year ( $\pm$  4 weeks) post administration of erenumab. All follow-up results, both positive and negative will be communicated to the sites. More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing is not required where it is established that the subject did not receive erenumab.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-erenumab antibody response may also be asked to return for additional follow-up testing. Refer to the Schedule of



Activities ([Table 2-1](#)), as applicable, for specific timepoints, and the laboratory manual for detailed collection and handling instructions.



#### **9.2.9 Clinical Outcome Assessments**

Refer to [Section 9.2.2](#) for COA details.

#### **9.2.10 Optional Substudies**

Up to 40 subjects will be asked to participate in an optional interview-based substudy. The substudy will be conducted at selected sites and will consist of a one-time qualitative telephone interview. Interviewers will attempt to conduct the interview as soon as possible and within 10 business days after Week 52 visit.

The telephone interview will last approximately 1 hour. The interviews will be conducted in local language by 3H Medi Solutions and audio-recorded. Audio files of the interviews will be transcribed and de-identified (ie, any identifying information such as names and locations will be removed). The de-identified transcripts will be translated for analysis; de-identified transcript will be kept as a source document in the trial master file. Copies of the audio file will be destroyed immediately upon confirmation of receipt of the final transcript.

The objective of the substudy is to (1) elicit a subject's perceptions of migraine, associated symptoms, and the impact/burden and interference of symptoms on a subject's life, (2) elicit a subject's perceptions of meaningful changes in experience of migraine, and (3) explore subject's experience with treatment administration. The relationship between headache and migraine attack and the

subject-level perception of treatment effect will also be explored and will help illustrate the subject's perspective of treatment response.

Subjects in the open-label phase will be invited to participate in the telephone interviews by the study investigators. A separate consent form will be requested for substudy inclusion. Information that explains participation in the interview process will be provided to the subjects. Acceptance to participate in the interviews will be documented on the informed consent form. Upon acceptance, subject contact details will be sent to 3H Medi Solutions. 3H Medi Solutions will be responsible for managing the interviews, scheduling, and interviewing the subjects.

During subject interviews, any adverse events reported by the subjects will be reported to the Investigator or designee by the interviewer within 1 business day. The Investigator will be responsible for reporting all adverse events, including those reported during the interviews following the process described in the protocol.

The results of this substudy will be reported separately from the main study.

Refer to [Appendix 8](#) for more information on the substudy.

#### 9.2.11 Other Assessments

Not applicable.

### 10. Statistical Considerations

#### 10.1 Sample Size Determination

The primary endpoint is the change from baseline in mean MMD over months 4, 5, and 6 of the DBTP.

[REDACTED]

[REDACTED] The treatment effect and variability are weighted based on treatment effect and variability estimates from Japanese EM Study 20120309 and pivotal global CM Study 20120295. Randomizing 256 subjects (128 subjects per treatment group, approximately 78 for EM and 50 for CM) will account for 10% dropout.

Furthermore, simulation of (global/Japanese/global and Japanese) erenumab data shows that the probability of achieving the point estimate of treatment difference

between erenumab and placebo (erenumab – placebo) < -1 MMD is [REDACTED], respectively (a  $\geq 1$  MMD reduction has been found clinically meaningful [Silberstein et al, 2010]). The joint probability of demonstrating statistical significance in the overall population and achieving the point estimate of treatment difference between erenumab and placebo < -1 MMD in both EM and CM subpopulations is [REDACTED] (Table 10-1).

**Table 10-1. Likelihood of Observing Greater MMD Reduction in Erenumab 70 mg Compared to Placebo in the EM/CM Subgroup**

	Sample Size <sup>a</sup>	
	140 EM Subjects (70 per group)	90 CM Subjects (45 per group)
Power for achieving statistical significance for the primary endpoint in overall population <sup>b</sup>	[REDACTED]	
Probability of achieving point estimate of treatment difference erenumab vs placebo < -1 MMD <sup>c</sup>	[REDACTED]	[REDACTED]
Joint probability of achieving both criteria above <sup>c</sup>	[REDACTED]	

CM = chronic migraine; EM = episodic migraine; MMD = monthly migraine days

<sup>a</sup> Not including 10% dropouts

<sup>b</sup> Based on the weighted average with the respective sample size of EM/CM subgroup, treatment difference (vs placebo) in overall population was estimated to be [REDACTED]

## 10.2 Analysis Sets, Subgroups, and Covariates

### 10.2.1 Analysis Sets

The full analysis set (FAS) includes all subjects who were randomized in the study. The efficacy analysis set includes subjects in the FAS and who received at least one dose of investigational product and had at least 1 change from baseline measurement in MMD during the DBTP. In the efficacy analysis set, subjects will be analyzed according to randomized treatment, regardless of the treatment received. For safety endpoints, all randomized subjects who received at least one dose of investigational product (ie, safety analysis set) will be analyzed according to the randomized treatment unless a subject has received the incorrect dose during the entire DBTP. The open-label analysis set (OLAS) will consist of all subjects receiving at least one dose of erenumab in the OLTP. This analysis set will be used when summarizing data collected during the OLTP.

### 10.2.2 Covariates

All analyses of efficacy endpoints will be adjusted for the effect of the stratification factors, including EM/CM and migraine preventive treatment status (ever used [prior and/or current] or never used), and the baseline value of the efficacy endpoint of interest.

### 10.2.3 Subgroups

The primary, secondary efficacy, and selected safety endpoints will be analyzed in the subgroups defined by the stratification factors as well as prior preventive treatment failure status (failed vs not failed [including never used]), and BMI (< median vs ≥ median).

### 10.2.4 Handling of Missing and Incomplete Data

Subjects may miss specific data points for a variety of causes. In general, data could be missing due to a subject's early withdrawal from study, a missed visit, or inability to evaluate an endpoint at a particular point in time. For this study, most of the efficacy endpoint will be collected via eDiary and subjects could miss entering several days of data in each monthly interval. The general procedures outlined below describe what will be performed when a data point is missing.

Missing eDiary data in the calculation of monthly measurements about subjects' migraine and non-migraine headaches will be handled using the following method.

- For each monthly interval with ≥ 14 days of eDiary use (including retrospective eDiary days):
  - Monthly frequency measurements (including migraine days, headache days, migraine attacks, and acute medication use) will be prorated to 28-day equivalents. Prorated result does not need to be rounded.

- For monthly intervals with < 14 days of eDiary use (including retrospective eDiary days), all monthly measurements will be set as missing.

Missing COAs [REDACTED] scheduled to be collected at office visit at certain assessment will not be imputed.

Missing safety endpoints will not be imputed. Missing or incomplete dates will be listed as reported, except for incomplete start date of an adverse event or concomitant medication, which will be imputed as follows:

Missing	Imputation	Exception
Day	01	Default to study day 1 if an adverse event started the same year and month as study day 1 and the flag indicates that the adverse event started on or after the first dose of investigational product on the Events electronic case report form (eCRF)
Day/Month	01 JAN	Default to study day 1 if an adverse event started the same year as study day 1 and the flag indicates that the adverse event started on or after the first dose of investigational product on the Events eCRF
Day/Month/Year	None	-

Missing PK and antibody data will not be imputed.

### **10.3 Statistical Analyses**

Below is a summary of the timing and methods for the planned statistical analyses.

#### **10.3.1 Planned Analyses**

##### **10.3.1.1 Primary Analysis**

The objective of the primary analysis is to evaluate the efficacy and safety of erenumab in subjects with EM or CM, compared to placebo. The primary analysis will be performed when the last subject completes the assessments for week 24 or the ET visit during DBTP, and all data are collected for the primary endpoint. At this time, the study will be unblinded to the sponsor and all efficacy and safety analyses will be conducted and reported by treatment group. Study subjects and investigators will remain blinded to the original DBTP assignment until study completion. Safety data collected during the OLTP before the data cutoff date for the primary analysis will also be summarized.

##### **10.3.1.2 Final Analysis**

The objective of the final analysis is to evaluate the long-term profile of MMD and adverse events of erenumab in subjects with migraine during the OLTP. The final analysis will be performed after all subjects have completed safety follow-up at the end of the study. Efficacy data and safety data from the OLTP will be tabulated by double-blind treatment group. No formal testing will be conducted.

#### **10.3.2 Methods of Analyses**

##### **10.3.2.1 General Considerations**

The primary objective of this study is to evaluate the effect of erenumab compared to placebo on the change from baseline in mean MMD over months 4, 5, and 6, in subjects with EM or CM.

Summary descriptive statistics by each treatment group will be tabulated at each visit. For continuous endpoints, the descriptive statistics include: number of observations, means, medians, SDs, SEs, first and third quartiles, and minimums and maximums. For categorical endpoints, the summaries will contain the number and percentage of subjects falling into each category. The number of days on investigational product and the total dose of investigational product will be summarized using descriptive statistics.

The FAS will be utilized to tabulate demographic data, baseline disease characteristics and subject disposition. The efficacy analysis set will be utilized to analyze efficacy endpoints. The safety analysis set will be used to analyze safety endpoints during the DBTP. The OLAS will be used to analyze the data collected during the OLTP.

Approved

### 10.3.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
<b>Primary</b>	<p>The primary endpoint, the change from baseline in mean MMD over months 4, 5, and 6 of the DBTP will be analyzed using the repeated measures linear mixed effects model including treatment group, baseline value, stratification factors, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data beyond proration of eDiary data per <a href="#">Section 10.2.4</a> under the missing-at-random (MAR) assumption on missing data mechanism. The LSM change from baseline with the 95% CI for each treatment group, the treatment difference (erenumab 70 mg – placebo) with the 95% CI, and p-value will be reported. The primary endpoint will be tested for erenumab 70 mg group compared to the placebo group at a 2-sided significance level of 0.05.</p> <p>In addition, the treatment difference with 95% CIs will also be provided for each of EM and CM subpopulations.</p> <p>Sensitivity analyses for the primary endpoint include: (1) the last observation carried forward (LOCF) to handle missing data with analysis of covariance (ANCOVA) model, and (2) multiple imputation with assumptions of MAR and missing not at random to handle missing data.</p>
<b>Secondary</b>	<ul style="list-style-type: none"> <li>Achievement of at least a 50% reduction from baseline in mean MMD over months 4, 5, and 6 of the DBTP</li> </ul> <p>The 50% responder endpoint will be analyzed using a stratified Cochran Mantel Haenszel (CMH) test after the missing data are imputed as non-response. The odds ratio for erenumab 70 mg group versus placebo group, associated 95% CI, and p-value will be reported. Sensitivity analyses for the binary endpoint include: (1) generalized linear mixed effects model without imputation of missing data beyond proration of eDiary data per <a href="#">Section 10.2.4</a> under the MAR assumption, and (2) logistic regression model for each visit after the missing data are imputed as non-responders.</p> <ul style="list-style-type: none"> <li>Change from baseline in mean monthly acute migraine-specific medication treatment days over months 4, 5, and 6 of the DBTP</li> </ul> <p>The same analysis methods will be used as for the primary endpoint.</p>
<b>Exploratory</b>	

### 10.3.2.3 Safety Analyses

All safety analyses will be performed for the DBTP and OLTP separately.

#### 10.3.2.3.1 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by treatment group and by system organ class and preferred term. Tables of fatal adverse

events, serious adverse events, adverse events leading to withdrawal from investigational product, and significant treatment-emergent adverse events will also be provided. Subject incidence of adverse device effects will be tabulated by system organ class and preferred term.

#### **10.3.2.3.2 Laboratory Test Results**

The analyses of safety laboratory endpoints will include summary statistics over time by treatment group for selected analytes. Shifts in grades of selected safety laboratory values between baseline and the worst on-study value will be tabulated by treatment group.

#### **10.3.2.3.3 Vital Signs**

The analyses of vital signs will include summary statistics over time by treatment group.

#### **10.3.2.3.4 Physical Measurements**

The analyses of physical measurements will include summary statistics over time by treatment group.

#### **10.3.2.3.5 Electrocardiogram**

The ECG measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

Subject incidence of abnormal ECG diagnosis will be summarized by treatment group.

#### **10.3.2.3.6 Antibody Formation**

The incidence and percentage of subjects who develop anti-erenumab antibodies (binding and if positive, neutralizing) at any time will be tabulated for subjects who received at least one dose of erenumab in the DBTP or OLTP.

#### **10.3.2.3.7 Exposure to Investigational Product**

The number and percentage of subjects receiving total number of investigational product doses and the number of days on investigational product will be summarized.

#### **10.3.2.3.8 Exposure to Concomitant Medication**

Number and percentage of subjects receiving headache-related medication will be summarized by category for each treatment group.

## 11. References

Amgen, Inc. Erenumab Investigator's Brochure. Thousand Oaks, CA.

Afridi SK, Giffin NJ, Kaube H, et al. A positron emission tomographic study in spontaneous migraine. *Arch Neurol*. 2005;62:1270-1275.

Aurora SK, Wilkinson F. The brain is hyperexcitable in migraine. *Cephalalgia*. 2007;27:1442-1453.

Aurora SK, Barrodale P, Chronicle EP, Mulleners WM. Cortical inhibition is reduced in chronic and episodic migraine and demonstrates a spectrum of illness. *Headache*. 2005;45:546-552.

Bellamy JL, Cady RK, Durham PL. Salivary levels of CGRP and VIP in rhinosinusitis and migraine patients. *Headache*. 2006;46:24-33.

Blumenfeld AW, Bloudek LM, Becker WJ, et al. Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second International Burden of Migraine Study (IBMS-II). *Headache*. 2013;53(4):644-655.

**Food and Drug Administration (FDA). Plan for Issuance of Patient-Focused Drug Development Guidance. 2017. Available at:**  
**<https://www.fda.gov/media/105979/download>.**

**Friese S, Ringmayr T. ATLAS.ti 7 User Guide and Reference. Berlin: ATLAS.ti Scientific Software Development GmbH; 2013.**

Gallai V, Sarchielli P, Floridi A, et al. Vasoactive peptide levels in the plasma of young migraine patients with and without aura assessed both interictally and ictally. *Cephalalgia*. 1995;15:384-390.

Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of Migraine: A Disorder of Sensory Processing. *Physiol Rev*. 2017;97(2):553-622.

Goadsby PG, Lipton RB, Ferrari MD. Migraine—current understanding and treatment. *N Engl J Med*. 2002;364(4):257-270.

Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann Neurol*. 1990;28:183-187.

Goadsby PJ, Edvinsson L, Ekman R. Release of vasoactive peptides in the extracerebral circulation of humans and the cat during activation of the trigeminovascular system. *Ann Neurol*. 1988;23:193-196.

Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd ed. *Cephalalgia*. 2018;38(1):1-211.

Ho TW, Connor KM, Zhang Y, et al. Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. *Neurology*. 2014;83:958-966.

Ho TW, Ferrari MD, Dodick DW, et al. Efficacy and tolerability of MK 0974 (telcagepant), a new oral antagonist of calcitonin gene related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo controlled, parallel treatment trial. *Lancet*. 2008a;372:2115-2123.



Ho TW, Mannix LK, Fan X, et al. MK 0974 Protocol 004 study group. Randomized controlled trial of an oral CGRP receptor antagonist, MK 0974, in acute treatment of migraine. *Neurology*. 2008b;70:1304-1312.

International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. 2013. <http://www.icmje.org/>

Juhasz G, Zsombok T, Jakab B, Nemeth J, Szolcsanyi J, Bagdy G. Sumatriptan causes parallel decrease in plasma calcitonin gene-related peptide (CGRP) concentration and migraine headache during nitroglycerin induced migraine attack. *Cephalalgia*. 2005;25(3):179-183.

Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olesen J. CGRP may play a causative role in migraine. *Cephalalgia*. 2002;22:54-61.

Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. AMPP Advisory Group: migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68:343-349.

Petersen KA, Lassen LH, Birk S, Lesko L, Olesen J. BIBN4096BS antagonizes human alpha-calcitonin gene related peptide-induced headache and extracerebral artery dilatation. *Clin Pharmacol Ther*. March 2005;77:202-213.

Sakai F, Igarashi H. Prevalence of migraine in Japan: a nationwide survey. *Cephalalgia*. 1997;17:15-22.

Sarchielli P, Pini LA, Zanchin G, et al. Clinical-biochemical correlates of migraine attacks in rizatriptan responders and non-responders. *Cephalalgia*. 2006;3:257-265.

Shimizu T. An overview of prophylactic therapy for migraine. *Brain Nerve*. 2009;61:1107-1115. [Article in Japanese]

Silberstein SD, Marmura MJ, Shaw J, et al. Headache prophylaxis with BoNRA: patient characteristics. *Headache*. 2010;40:63-70.

Stovner LJ, Andree C. Prevalence of headache in Europe: a review for the Eurolight project. *J Headache Pain*. 2010;11(4):289-299.

Sun H, Dodick DW, Silberstein S, et al. Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol*. 2016;15(4):382-390.

Tajti J, Uddman R, Möller S, Sundler F, Edvinsson L. Messenger molecules and receptor mRNA in the human trigeminal ganglion. *J Auton Nerv Syst*. 1999;76:176-183.

Tassorelli C, Diener H, Dodick D, et al. Guidelines of the International Headache Society for controlled trials of preventive treatment of chronic migraine in adults. *Sage Journal*. 2018;38:815-832.

Tfelt-Hansen P, Pascual J, Ramadan N, et al. Guidelines for controlled trials of drugs in migraine: Third edition. A guide for investigators. *Cephalalgia*. 2012;32(1):6-38.

Welch KM, Nagesh V, Aurora S, Gelman N. Periaqueductal gray matter dysfunction in migraine and chronic daily headache may be due to free radical damage. *J Headache Pain*. 2001;2(Suppl 1):33-41.

Approved

**12. Appendices**

Approved

## 12.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BDI	Beck Depression Inventory
BIL	bilirubin
BMI	body mass index
CFR	Code of Federal Regulations
CGRP	calcitonin gene-related peptide
CHO	Chinese hamster ovary
CI	confidence interval
CM	chronic migraine
CMH	Cochran Mantel Haenszel
COA	clinical outcome assessment
CRF	case report form
C-SSRS	Columbia-suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DBTP	double-blind treatment period
DILI	drug induced liver injury
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EM	episodic migraine
EMA	European Medicines Agency
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
ET	early termination
FAS	full analysis set
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HepBcAb	hepatitis B core antibody
HepBsAg	hepatitis B surface antigen
HRT	hormonal replacement therapy
ICF	informed consent form

Approved

Abbreviation or Term	Definition/Explanation
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG2	immunoglobulin G2
IHS	International Headache Society
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
Interactive <b>Response Technology</b> System (IRT)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information
LOCF	last observation carried forward
LSM	least squares means
MAR	missing-at-random
MI	myocardial infarction
MMD	monthly migraine days
NCT	National Clinical Trials
OLAS	open-label analysis set
OLTP	open-label treatment period
PCR	polymerase chain reaction
PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PRO	Patient-reported Outcome
Q4W	every 4 weeks
QM	once monthly
SC	subcutaneously
SD	standard deviation
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.

Approved

Abbreviation or Term	Definition/Explanation
study day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
TBL	total bilirubin
TIA	transient ischemic attack
ULN	upper limit of normal
US	United States

Approved

## **12.2            Appendix 2. Clinical Laboratory Tests**

The tests detailed in [Table 12-1](#) will be performed by the central laboratory and/or by the local laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the case report form (CRF).

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in [Sections 6.1](#) to [6.4](#) of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Approved

**Table 12-1. Analyte Listing**

Central Laboratory: Chemistry	Central Laboratory: Urinalysis	Central Laboratory: Hematology	Other Labs
Sodium	Specific gravity	RBC	<u>Central Laboratory:</u>
Potassium	pH	Nucleated RBC	
Chloride	Blood	Hemoglobin	
Bicarbonate	Protein	Hematocrit	Anti-erenumab antibodies
Total protein	Glucose	MCV	
Albumin	Bilirubin	MCH	
Calcium	WBC	MCHC	Hep B surface antigen <sup>a</sup>
Adjusted calcium	RBC	RDW	Hep B core antibody <sup>a</sup>
Magnesium	Epithelial cells	Reticulocytes	Hep C antibody <sup>a</sup>
Phosphorus	Bacteria	Platelets	Serum pregnancy
Glucose	Casts	WBC	
BUN or Urea	Crystals	Differential	<u>Local Laboratory:</u>
Creatinine		• Bands/stabs	Urine Pregnancy
Total bilirubin		• Segmented neutrophils	
Direct bilirubin		• Total neutrophils	
ALP		• Eosinophils	
LDH		• Basophils	
AST (SGOT)		• Lymphocytes	
ALT (SGPT)		• Monocytes	
		• Myeloblasts	
		• Promyelocytes	
		• Myelocytes	
		• Metamyelocytes	
		• Atypical lymphocytes	

<sup>a</sup> A blood sample will be collected and stored during screening. Hepatitis testing will only be performed if a hepatic event is suspected during the study.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Hep = hepatitis; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RDW = red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

## **12.3 Appendix 3. Study Governance Considerations**

### **Independent Review Committee**

Not applicable.

### **Regulatory and Ethical Considerations**

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the United States (US) Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations



## **Informed Consent Process**

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to [Section 8](#).

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

The informed consent form (ICF) will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

#### **Data Protection/Subject Confidentiality**

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the case report form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

### **Publication Policy**

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals [International Committee of Medical Journal Editors \(2013\)](#) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All

persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

### **Investigator Signatory Obligations**

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- a recognized expert in the therapeutic area
- an Investigator who provided significant contributions to either the design or interpretation of the study
- an Investigator contributing a high number of eligible subjects

### **Data Quality Assurance**

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research and Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

Case report forms must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

### **Source Documents**

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the Interactive **Response Technology** (IRT) system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording

(ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the [IRB/IEC] and Amgen
- Investigational product-related correspondence including Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Non-investigational product(s), and/or medical device(s), or combination product(s) documentation, as applicable

Retention of study documents will be governed by the Clinical Trial Agreement.

### **Study and Site Closure**

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine

whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

### **Compensation**

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

Approved

## 12.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

### Definition of Adverse Event

Adverse Event Definition
<ul style="list-style-type: none"><li>An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment.</li><li>Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure.</li></ul>
Events Meeting the Adverse Event Definition
<ul style="list-style-type: none"><li>Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).</li><li>Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.</li><li>New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.</li><li>Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.</li><li>Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae.</li><li>"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.</li></ul>
Events NOT Meeting the Adverse Event Definition
<ul style="list-style-type: none"><li>Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event.</li><li>Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).</li><li>Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.</li></ul>

Approved



## Definition of Serious Adverse Event

<b>A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:</b>
<b>Results in death (fatal)</b>
<b>Immediately life-threatening</b> The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
<b>Requires in-patient hospitalization or prolongation of existing hospitalization</b> In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
<b>Results in persistent or significant disability/incapacity</b> The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
<b>Is a congenital anomaly/birth defect</b>
<b>Other medically important serious event</b> Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Approved

## Definition of Adverse Device Effect

The detection and documentation procedures for adverse device effects described in this protocol apply to all Amgen medical devices provided for use in the study (see [Section 7.1.3](#) for the list of Amgen medical devices).

### Adverse Device Effect Definition

An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

## Recording Adverse Events, Disease-related Events (if applicable), and Serious Adverse Events

### Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/serious adverse event information in the Event case report form (CRF).
- The investigator must assign the following adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Severity (or toxicity defined below);
  - Assessment of relatedness to investigational product (erenumab or placebo) or Amgen medical devices (prefilled syringe); and
  - Action taken.
- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event CRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor in lieu of completion of the Event CRF page.
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

## Evaluating Adverse Events and Serious Adverse Events

### Assessment of Severity

The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:

The Common Terminology Criteria for Adverse Events, version 4.0 which is available at the following location: [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

### Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product and device and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

### Follow-up of Adverse Event and Serious Adverse Event

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed Event CRF.
- The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

## Reporting of Serious Adverse Event

### Serious Adverse Event Reporting via Electronic Data Collection Tool

- The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system via the Safety Report Form.
- If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an electronic Serious Adverse Contingency Report Form (see [Figure 12-1](#)) within 24 hours of the investigator's knowledge of the event.
- The site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on a paper Serious Adverse Event Report Form (see [Figure 12-1](#)).

### Adverse Device Effects: Recording, Evaluating and Reporting

- Any adverse event resulting from an adverse device effect that occur during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the Event CRF page.
- It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by Amgen) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident.

Approved

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Form

<b>AMGEN</b> Study # 20170609 (erenumab/AMG 334)		<b>Electronic Serious Adverse Event Contingency Report Form</b> <b>For Restricted Use</b>																										
<b>Reason for reporting this event via fax</b> The Clinical Trial Database (eg, Rave): <input type="checkbox"/> Is not available due to internet outage at my site <input type="checkbox"/> Is not yet available for this study <input type="checkbox"/> Has been closed for this study																												
<< FAX # : 0120-077-507 >>																												
<b>1. SITE INFORMATION</b>																												
Site Number 		Investigator 				Country 																						
Reporter 		Phone Number (     )				Fax Number (     )																						
<b>2. SUBJECT INFORMATION</b>																												
Subject ID Number 		Age at event onset 		Sex <input type="checkbox"/> F <input type="checkbox"/> M		Race 		If applicable, provide End of Study date 																				
If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____ and start date: Day ____ Month ____ Year ____																												
<b>3. SERIOUS ADVERSE EVENT</b>																												
Provide the date the investigator became aware of this information: Day ____ Month ____ Year ____																												
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td rowspan="2" style="width: 30%;">           Serious Adverse Event <u>diagnosis</u> or syndrome            If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report            List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.         </td> <td style="width: 10%;">           Date Started            Day Month Year         </td> <td style="width: 10%;">           Date Ended            Day Month Year         </td> <td style="width: 5%;">           Check only if event occurred before first dose of IP         </td> <td style="width: 5%;">           Is event serious?  <input type="checkbox"/> Yes  <input type="checkbox"/> No         </td> <td style="width: 10%;">           Is serious enter Serious Criteria code (see codes below)         </td> <td colspan="2" style="width: 20%;">           Relationship            Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP?         </td> <td style="width: 10%;">           Outcome of Event            -Resolved            -Not resolved            -Fatal            -Unknown         </td> <td style="width: 10%;">           Check only if event is related to study procedure            eg, biopsy         </td> </tr> <tr> <td colspan="2"></td> <td colspan="2"></td> <td colspan="2"></td> <td colspan="2"></td> <td></td> </tr> </table>										Serious Adverse Event <u>diagnosis</u> or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious? <input type="checkbox"/> Yes <input type="checkbox"/> No	Is serious enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP?		Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy									
Serious Adverse Event <u>diagnosis</u> or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious? <input type="checkbox"/> Yes <input type="checkbox"/> No	Is serious enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP?		Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy																			
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td rowspan="2" style="width: 15%;">           Serious Criteria:            01 Fatal            02 Immediately life-threatening         </td> <td rowspan="2" style="width: 15%;">           03 Required/prolonged hospitalization            04 Persistent or significant disability /incapacity         </td> <td rowspan="2" style="width: 15%;">           05 Congenital anomaly / birth defect            06 Other medically important serious event         </td> <td colspan="7"></td> </tr> <tr> <td colspan="7"></td> </tr> </table>										Serious Criteria: 01 Fatal 02 Immediately life-threatening	03 Required/prolonged hospitalization 04 Persistent or significant disability /incapacity	05 Congenital anomaly / birth defect 06 Other medically important serious event																
Serious Criteria: 01 Fatal 02 Immediately life-threatening	03 Required/prolonged hospitalization 04 Persistent or significant disability /incapacity	05 Congenital anomaly / birth defect 06 Other medically important serious event																										
<b>4. Was subject hospitalized or was a hospitalization prolonged due to this event?</b> <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete all of Section 4																												
Date Admitted Day Month Year					Date Discharged Day Month Year																							
<b>5. Was IP/drug under study administered/taken prior to this event?</b> <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete all of Section 5																												
IP/Amgen Device:		<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th colspan="6">Prior to, or at time of Event</th> <th rowspan="2">Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld</th> <th rowspan="2">Lot # and Serial #</th> </tr> <tr> <th>Date of Initial Dose Day Month Year</th> <th>Date of Dose Day Month Year</th> <th>Dose</th> <th>Route</th> <th>Frequency</th> <th></th> </tr> </table>								Prior to, or at time of Event						Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #	Date of Initial Dose Day Month Year	Date of Dose Day Month Year	Dose	Route	Frequency						
		Prior to, or at time of Event						Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #																			
Date of Initial Dose Day Month Year	Date of Dose Day Month Year	Dose	Route	Frequency																								
Erenumab (AMG 334) <input type="checkbox"/> blinded <input type="checkbox"/> open label																												
Amgen Prefilled Syringe (PFS) <input checked="" type="checkbox"/> open label																												

FORM-056006

Page 1 of 3

Version 7.0 Effective Date: 1 February 2016

Approved

Approved

<b>AMGEN</b> Study # 20170609 (erenumab/AMG 334)		<b>Electronic Serious Adverse Event Contingency Report Form</b> <b>For Restricted Use</b>													
		Site Number				Subject ID Number									
<b>10. CASE DESCRIPTION</b> ( <i>Provide narrative details of events listed in section 3</i> ) Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.															
Signature of Investigator or Designee –  <i>I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.</i>										Title			Date		

Approved

## 12.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for female subjects of childbearing potential are outlined in [Section 6.2](#).

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and for 12 weeks after the last dose of protocol-required therapies.

### Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - documented hysterectomy;
  - documented bilateral salpingectomy; or
  - documented bilateral oophorectomy.

Note: Site personnel documentation from the following sources is acceptable:

- 1) review of subject's medical records;
- 2) subject's medical examination; or
- 3) subject's medical history interview.

- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

### Contraception Methods for Female Subjects

#### Acceptable Methods of Effective Contraception

- combined (estrogen and progestogen containing) or progestogen-only hormonal methods: oral
- intrauterine device (IUD)



- intrauterine hormonal-releasing system (IUS)
- bilateral tubal ligation
- vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- male or female condom with or without spermicide
- cap **or** diaphragm
- double-barrier method: the male uses a condom and the female may choose either a cap **or** diaphragm (a female condom is not an option due to the risk of tearing when both partners use a condom)

### **Unacceptable Methods of Birth Control for Female Subjects**

Birth control methods that are considered unacceptable in clinical trials include:

- periodic abstinence (calendar, symptothermal, post-ovulation methods)
- withdrawal (coitus interruptus)
- spermicides only
- lactational amenorrhea method

### **Collection of Pregnancy Information**

#### Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 12 weeks after the last dose of study drug.
- Information will be recorded on the Pregnancy Notification Worksheet (see [Figure 12-2](#)). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 12 weeks after the last dose of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death, or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a poststudy pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in [Section 12.4](#). While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see [Section 8.1](#) for details).

#### **Male Subjects With Partners Who Become Pregnant**

- In the event a male subject fathers a child during treatment, and for an additional 12 weeks after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see [Figure 12-2](#)) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Approved

---

### **Collection of Lactation Information**

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 12 weeks after the last dose of study drug.
- Information will be recorded on the Lactation Notification Worksheet (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in [Exclusion Criterion 225](#).
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through the last dose of study drug after discontinuing protocol-required therapies.

Approved

Figure 12-2. Pregnancy and Lactation Notification Worksheets

**AMGEN®** Pregnancy Notification Worksheet  
*Fax Completed Form to the Country-respective Safety Fax Line*  
FAX# 0120-077-507

**1. Case Administrative Information**  
Protocol/Study Number: 20170609  
Study Design: ☒ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

**2. Contact Information**  
Investigator Name \_\_\_\_\_ Site # \_\_\_\_\_  
Phone (\_\_\_\_) \_\_\_\_\_ Fax (\_\_\_\_) \_\_\_\_\_ Email \_\_\_\_\_  
Institution \_\_\_\_\_  
Address \_\_\_\_\_

**3. Subject Information**  
Subject ID # \_\_\_\_\_ Subject Gender: ☐ Female ☐ Male Subject DOB: mm \_\_\_\_ / dd \_\_\_\_ / yyyy \_\_\_\_

**4. Amgen Product Exposure**

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm ____ / dd ____ / yyyy ____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No  
If yes, provide product (or study drug) stop date: mm \_\_\_\_ / dd \_\_\_\_ / yyyy \_\_\_\_  
Did the subject withdraw from the study? ☐ Yes ☐ No

**5. Pregnancy Information**

Pregnant female's LMP mm \_\_\_\_ / dd \_\_\_\_ / yyyy \_\_\_\_ ☐ Unknown  
Estimated date of delivery mm \_\_\_\_ / dd \_\_\_\_ / yyyy \_\_\_\_ ☐ Unknown ☐ N/A  
If N/A, date of termination (actual or planned) mm \_\_\_\_ / dd \_\_\_\_ / yyyy \_\_\_\_  
Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A  
If yes, provide date of delivery: mm \_\_\_\_ / dd \_\_\_\_ / yyyy \_\_\_\_  
Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A  
If any Adverse Event was experienced by the infant, provide brief details: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**Form Completed by:**  
Print Name: \_\_\_\_\_ Title: \_\_\_\_\_  
Signature: \_\_\_\_\_ Date: \_\_\_\_\_

\*\*\*\*\*

Effective Date: March 27, 2011Page 1 of 1

Approved

**AMGEN®** Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

0120-077-507

**1. Case Administrative Information**

Protocol/Study Number: 20170609

Study Design: ☒ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

**2. Contact Information**

Investigator Name \_\_\_\_\_ Site # \_\_\_\_\_  
Phone (\_\_\_\_) \_\_\_\_\_ Fax (\_\_\_\_) \_\_\_\_\_ Email \_\_\_\_\_  
Institution \_\_\_\_\_  
Address \_\_\_\_\_

**3. Subject Information**

Subject ID # \_\_\_\_\_ Subject Date of Birth: mm \_\_\_\_ / dd \_\_\_\_ / yyyy \_\_\_\_

**4. Amgen Product Exposure**

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm ____ / dd ____ / yyyy ____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm \_\_\_\_ / dd \_\_\_\_ / yyyy \_\_\_\_

Did the subject withdraw from the study? ☐ Yes ☐ No

**5. Breast Feeding Information**

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm \_\_\_\_ / dd \_\_\_\_ / yyyy \_\_\_\_

Infant date of birth: mm \_\_\_\_ / dd \_\_\_\_ / yyyy \_\_\_\_

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**Form Completed by:**

Print Name: \_\_\_\_\_

Title: \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

## **12.6 Appendix 6. Sample Storage and Destruction**

Any blood or pharmacokinetics (PK) sample collected according to the Schedule of Activities (Table 2-1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the migraine, the dose response and/or prediction of response to erenumab, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of [REDACTED], or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood, PK samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as

appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See [Section 12.3](#) for subject confidentiality.

Approved

## **12.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines**

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

### **Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity**

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- hepatobiliary tract disease
- viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- right-sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin (BIL) glucuronidation (eg, indinavir, atazanavir)
- alpha-one antitrypsin deficiency
- alcoholic hepatitis
- autoimmune hepatitis
- Wilson's disease and hemochromatosis
- nonalcoholic fatty liver disease including steatohepatitis
- non-hepatic causes (eg, rhabdomyolysis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible drug induced liver injury (DILI) according to recommendations in the last section of this appendix.



Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

**Table 12-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity**

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3 x ULN at any time	> 2 x ULN
INR	--	OR > 1.5 x (for subjects not on anticoagulation therapy)
AST/ALT	OR > 8 x ULN at any time > 5 x ULN but < 8 x ULN for ≥ 2 weeks > 5 x ULN but < 8 x ULN and unable to adhere to enhanced monitoring schedule > 3 x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	AND In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3 x ULN (when baseline was < ULN)
ALP	OR > 8x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

#### Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then Amgen investigational product is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in [Table 12-2](#)) are never to be rechallenged.

## **Drug-induced Liver Injury Reporting and Additional Assessments**

### Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified in the above, require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate case report form (CRF) (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in [Section 12.4](#).

### Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in [Table 12-2](#) or who experience AST or ALT elevations  $> 3 \times$  upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (BIL) (total and direct), and INR within 24 hours
- In cases of TBL  $> 2 \times$  ULN or INR  $> 1.5$ , retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL.

The following are to be considered depending on the clinical situation:

- complete blood count with differential to assess for eosinophilia
- serum total immunoglobulin (Ig)G, anti-nuclear antibody, anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- serum acetaminophen (paracetamol) levels

- a more detailed history of:
  - prior and/or concurrent diseases or illness
  - exposure to environmental and/or industrial chemical agents
  - symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - prior and/or concurrent use of alcohol, recreational drugs and special diets
  - concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- viral serologies
- creatine phosphokinase, haptoglobin, lactate dehydrogenase and peripheral blood smear
- appropriate liver imaging if clinically indicated
- appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding CRFs.

Approved

**12.8 Appendix 8. Substudy: Qualitative Interview Substudy to “A Phase 3 Japanese Randomized, Double Blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention”.**

**Substudy Background and Rationale**

Qualitative interviews enable access to qualitative aspects of experiences of clinical trial participants to supplement the quantitative data collected as part of the study. For example, treatment satisfaction can be assessed to understand which aspects of the treatment are valued by subjects such as symptom benefit, delivery method, and adverse event tolerability. Interviewing clinical trial participants at the end of the treatment period can also help identify benefits most relevant and meaningful to subjects. This can also complement and help interpret the quantitative data collected using COA instruments in the clinical trial.

Regulatory agencies are showing increasing interest in understanding subjects’ experiences of the risk-benefit related to new interventions being tested in clinical trials ([FDA, 2017](#)). Qualitative interviews at the end of clinical trials help to understand the subjects’ experience of the treatment in the trial setting: their experience of the convenience of treatment, changes they perceive as result of treatments, and informal assessments of trade-offs on benefit and risks they perceive about the treatment.

**Research Question and Objective(s) of the Qualitative Interview Substudy**

The aim of this study is to collect qualitative data to assess the experience of treatment from a subset of adults with EM and CM who have participated in Study 20170609 to provide a more in-depth understanding of subjects’ experience with migraine and the impact of migraine, including perception of symptoms and burden of disease. The objectives are to elicit subject’s perceptions of migraine, associated symptoms, and symptom impact/burden and interference on subject’s life, patient perceptions of meaningful changes in experience of migraine and to explore subject’s experience with treatment administration.

**Substudy Design**

One-time qualitative telephone interviews will be conducted with subjects who consent to this substudy. Exit interviews will be conducted as soon as possible and within 10 business days after Week 52 visit.

## **Summary of Substudy Subject Participation Criteria**

**Study subjects must meet the following criteria to be considered for enrollment into the substudy:**

- 1) Completed the investigational product in both treatment periods as indicated on the respective end of investigational product eCRF (may miss up to 1 dose during each phase);**
- 2) Have provided supplementary informed consent to participate in the substudy;**
- 3) Be willing and able to participate in a telephone interview lasting approximately 1 hour;**
- 4) Be able to read, understand, and speak Japanese sufficiently to participate in the interviews;**
- 5) Be willing to be audio-recorded during the interview sessions.**

**Meeting any of the following criterion will exclude a subject from enrollment into the substudy:**

- 1) Unable to complete interview within 10 business days of the Week 52 visit**
- 2) Has any clinically relevant medical or psychiatric condition that, in the opinion of the investigator and/or study coordinator, would interfere with the completion of the substudy activities. This includes but is not limited to language, speech, hearing or cognitive disorders that could impact a subject's ability to participate in an interview-based discussion.**

## **Substudy Duration and Substudy Procedures**

**Subjects are required to participate in 1 telephone interview, lasting approximately 1 hour. Interviews will be conducted as soon as possible after the week 52 visit, but within 10 business days of the visit.**

**Subjects enrolled in the clinical trial 20170609 will be approached by clinic staff for recruitment and possible enrollment into this substudy.**

**At participating sites, randomized subjects that are successfully dosed (may miss up to 1 dose during each phase) with investigational product (DBTP and OLTP) will be provided an option to participate in the qualitative interview substudy and be provided with additional information about the substudy. Clinical site staff will**

explain the substudy objectives and procedures to the subject and obtain a supplementary written informed consent. The signature process for this informed consent will be the same as the informed consent for the main study.

Once consent has been obtained, the subject ID and site details can be communicated by the site to the interview scheduler from 3H Medi Solutions along with potential dates for the Week 52 visit. The interview scheduler will obtain subject contact information and schedule a tentative date and time for the interview with the participant. 3H Medi Solutions will confirm with the site that the subject has completed study procedures for the Week 52 visit before confirming the interview date and time of the interview with the subject to ensure compliance to the substudy protocol.

The subject must personally sign and date the IRB/IEC-approved substudy informed consent before commencement of substudy-specific procedures. A subject is considered enrolled in the substudy when the investigator decides that the subject has met the substudy participation criteria and subject has signed and dated the substudy informed consent. The interviewer will not interview the subject until 3H Medi Solutions receives written confirmation from sites of completion of week 52 study procedures.

3H Medi Solutions staff, who are trained and experienced in qualitative data collection, will conduct telephone interviews using a semi-structured interview guide (in local language). Subjects will be interviewed about their pre-treatment status and any perceived changes since the start of the open-label phase of treatment; ie, from the time they were informed they were being administered Erenumab.

Subjects will be interviewed about the changes experienced and the meaningfulness of the changes experienced. During the interviews, interviewers will ask subjects for specific examples to qualitatively illustrate the subjects' experience.

Subjects will be specifically asked about their experiences with functioning during and between migraine attacks after the start of the open-label phase; ie, perceptions of migraine, associated symptoms, and symptom impact/burden and interference on their life; perceptions of meaningful changes in experience of migraine; experience with treatment administration.

After open-ended questions, if subjects do not mention concepts associated with the domains of the COA instrument in the clinical trial, the interviewer will specifically probe about those concepts. The interviewers will also explore what aspects of improvement or worsening of their migraine (eg, frequency, severity, and duration) drove the changes, as well as the meaningfulness of change/no change reported by the subject.

#### **Variables**

##### **Substudy Outcome Variable(s)**

Qualitative data on changes resulting from treatment received in the open-label extension will be collected via telephone interview. Concepts that emerge from the qualitative interviews in relation to migraine impact, treatment efficacy, and migraine experience will be the outcome. Data will be analyzed to achieve the study objectives, using qualitative data analysis software (ie, ATLAS.ti). Upon unblinding as outlined in the parent protocol, the clinical trial data may be further used to explore response perceptions.

##### **Exposure Variable(s)**

Subjects will be randomized to placebo or erenumab 70 mg (1:1) SC injections every 4 weeks in the DBTP; during open-label extension of study protocol 20170609, all subjects will receive erenumab 70 mg. Interviewers and subjects will be blinded to the treatment that subjects were administered during the parent clinical trial.

##### **Substudy Sample Size**

The substudy sample size is based on a convenience sample to allow for sufficient numbers of EM and CM subjects enrolled.

The substudy sample will be a subset of up to 40 subjects who will be recruited from up to 6 clinical sites participating in the clinical trial 20170609 across Japan.

##### **Substudy Data Analysis**

Audio recordings from the interviews will be transcribed for qualitative analyses. Evidera will develop a separate data analysis plan that will detail how the qualitative data will be analyzed. The analyses of interview data will help to illustrate subjects' perceptions of meaningful change or difference, migraine functional impacts, and treatment efficacy or benefit. The qualitative report will

discuss (1) subject-reported perceptions of migraine, associated symptoms, and symptom impact/burden and interference on subject's life, (2) subject's perceptions of meaningful changes in experience of migraine and (3) subject's experience with treatment administration.

A qualitative content analysis approach will be used to analyze data collected from qualitative interviews using coding dictionaries and ATLAS.ti qualitative data analysis software. The cleaned transcripts will be entered into ATLAS.ti qualitative analysis software version 7.0 or higher ([Friese and Ringmayr, 2013](#)). Qualitative data coded in ATLAS.ti can be systematically organized into analysis outputs. ATLAS.ti software is designed to facilitate the storage, coding, and retrieval of qualitative data.

Coding will be an iterative process that marks the beginning of the qualitative analysis process. Concept codes will be used to capture symptoms or impacts of the disease most important and relevant to participants. Qualitative data will be coded according to the coding dictionary as outlined in the analysis plan. The initial coding dictionary will be based on the structure of the main themes and content of discussion guide to allow the text data to be coded with key concepts codes. The coding dictionary will be iteratively updated with emerging themes and concepts from discussions.

All analysis and reporting will be conducted by Evidera staff with experience in qualitative research.

Subject characteristics collected in the clinical trial will be summarized for describing the sample. Descriptive statistics (eg, n, mean, SD, and/or frequency) will be used to characterize the sample in terms of questionnaire data, sociodemographic, and clinical characteristics.

#### Collection of Safety Information and Product Complaints

There will be no substudy-specific safety database for collection, recording, and reporting of adverse events reported during the conduct of the substudy. All safety data collection, recording, and reporting will be performed through the parent study and will follow the detailed procedures outlined in study protocol 20170609. Adverse events, serious adverse events, or product complaints reported during the conduct of an interview will be reported to Amgen and to investigational sites within 1 business day of awareness.



## **Definition of Safety Events**

Refer to [Section 9.2.3.1](#) of the parent protocol for definition of safety events.

## **Safety Reporting Requirements**

The clinical site Investigator is responsible for ensuring that safety events (adverse events, product complaints, and other safety findings) are reported in accordance with Amgen's clinical trial 20170609 protocol. 3H Medi Solutions will notify the clinical site and Amgen with any report of adverse events to complete the adverse event data collection into the Study 20170609 database. 3H Medi Solutions will report any adverse events to the clinical site and Amgen within 1 business day of awareness; the site Investigator will be responsible for reconciling the reporting to Amgen.

Safety events must be submitted by the clinical site Investigator as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) which will be the responsibility of the subject's clinic site in accordance with clinical trial 20170609 protocol.

Approved

**Amendment 2**

**Protocol Title: A Phase 3 Japanese Randomized, Double-blind,  
Placebo-controlled Study to Evaluate the Efficacy and Safety of Erenumab in  
Migraine Prevention**

Amgen Protocol Number Erenumab 20170609

NCT number: NCT03812224

Amendment Date: 02 December 2019

**Rationale:**

This protocol is being amended to

- add a substudy
- to replace “Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) system” with “Interactive Response Technology (IRT)”.

Approved

**Description of Changes:**

[Section: Global](#)

**Change:** The Amgen global version date was changed from 19 December 2018 to **02 December 2019**.

[Section: Global](#)

**Replace:**

Interactive Voice Response System (IVRS) / Interactive Web Response System (IWRS) system.

**With:**

**Interactive Response Technology (IRT).**

[Section: Title Page](#)

**Replace:**

NCT Number:	Unavailable for first version	
Protocol Date:	<u>Document Version</u>	<u>Date</u>
	Original	10 September 2018
	Amendment 1	19 December 2018

**With:**

NCT Number:	<b>NCT03812224</b>	
Protocol Date:	<u>Document Version</u>	<u>Date</u>
	Original	10 September 2018
	Amendment 1	19 December 2018
	<b>Amendment 2</b>	<b>02 December 2019</b>

Approved

Section: 2.2 Schedule of Activities, Table 2-3 Schedule of Activities – Optional Interview-based Substudy

Add:

Table 2-3. Schedule of Activities – Optional Interview-based Substudy

Procedure	Week 48-52	Week 52
Substudy informed consent	X <sup>a</sup>	
Substudy Participation Requirements	X <sup>a</sup>	
Interview <sup>b</sup>		X

<sup>a</sup> Signing of informed consent and participation screening can occur any time at or after the Week 48 visit.

<sup>b</sup> Interviewers will attempt to conduct the interview as soon as possible and within 10 business days after Week 52 visit.

Approved

**Section:** 9.2.10 Optional Substudies

**Replace:**

Not applicable.

**With:**

Up to 40 subjects will be asked to participate in an optional interview-based substudy. The substudy will be conducted at selected sites and will consist of a one-time qualitative telephone interview. Interviewers will attempt to conduct the interview as soon as possible and within 10 business days after Week 52 visit.

The telephone interview will last approximately 1 hour. The interviews will be conducted in local language by 3H Medi Solutions and audio-recorded. Audio files of the interviews will be transcribed and de-identified (ie, any identifying information such as names and locations will be removed). The de-identified transcripts will be translated for analysis; de-identified transcript will be kept as a source document in the trial master file. Copies of the audio file will be destroyed immediately upon confirmation of receipt of the final transcript.

The objective of the substudy is to (1) elicit a subject's perceptions of migraine, associated symptoms, and the impact/burden and interference of symptoms on a subject's life, (2) elicit a subject's perceptions of meaningful changes in experience of migraine, and (3) explore subject's experience with treatment administration. The relationship between headache and migraine attack and the subject-level perception of treatment effect will also be explored and will help illustrate the subject's perspective of treatment response.

Subjects in the open-label phase will be invited to participate in the telephone interviews by the study investigators. A separate consent form will be requested for substudy inclusion. Information that explains participation in the interview process will be provided to the subjects. Acceptance to participate in the interviews will be documented on the informed consent form. Upon acceptance, subject contact details will be sent to 3H Medi Solutions. 3H Medi Solutions will be responsible for managing the interviews, scheduling, and interviewing the subjects.

During subject interviews, any adverse events reported by the subjects will be reported to the Investigator or designee by the interviewer within 1 business day.

The Investigator will be responsible for reporting all adverse events, including those reported during the interviews following the process described in the protocol.

The results of this substudy will be reported separately from the main study. Refer to Appendix 8 for more information on the substudy.

Section: 11 References

Add:

Food and Drug Administration (FDA). Plan for Issuance of Patient-Focused Drug Development Guidance. 2017. Available at: <https://www.fda.gov/media/105979/download>.

Friese S, Ringmayr T. ATLAS.ti 7 User Guide and Reference. Berlin: ATLAS.ti Scientific Software Development GmbH; 2013.

Section: 12.8 Appendix 8 (new section)

Add:

Appendix 8. Substudy: Qualitative Interview Substudy to “A Phase 3 Japanese Randomized, Double blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention”.

Substudy Background and Rationale

Qualitative interviews enable access to qualitative aspects of experiences of clinical trial participants to supplement the quantitative data collected as part of the study. For example, treatment satisfaction can be assessed to understand which aspects of the treatment are valued by subjects such as symptom benefit, delivery method, and adverse event tolerability. Interviewing clinical trial participants at the end of the treatment period can also help identify benefits most relevant and meaningful to subjects. This can also complement and help interpret the quantitative data collected using COA instruments in the clinical trial.

Regulatory agencies are showing increasing interest in understanding subjects’ experiences of the risk-benefit related to new interventions being tested in clinical trials (FDA, 2017). Qualitative interviews at the end of clinical trials help to understand the subjects’ experience of the treatment in the trial setting: their experience of the convenience of treatment, changes they perceive as result of treatments, and informal assessments of trade-offs on benefit and risks they perceive about the treatment.

## **Research Question and Objective(s) of the Qualitative Interview Substudy**

The aim of this study is to collect qualitative data to assess the experience of treatment from a subset of adults with EM and CM who have participated in Study 20170609 to provide a more in-depth understanding of subjects' experience with migraine and the impact of migraine, including perception of symptoms and burden of disease. The objectives are to elicit subject's perceptions of migraine, associated symptoms, and symptom impact/burden and interference on subject's life, patient perceptions of meaningful changes in experience of migraine and to explore subject's experience with treatment administration.

## **Substudy Design**

One-time qualitative telephone interviews will be conducted with subjects who consent to this substudy. Exit interviews will be conducted as soon as possible and within 10 business days after Week 52 visit.

## **Summary of Substudy Subject Participation Criteria**

Study subjects must meet the following criteria to be considered for enrollment into the substudy:

- 1) Completed the investigational product in both treatment periods as indicated on the respective end of investigational product eCRF (may miss up to 1 dose during each phase);
- 2) Have provided supplementary informed consent to participate in the substudy;
- 3) Be willing and able to participate in a telephone interview lasting approximately 1 hour;
- 4) Be able to read, understand, and speak Japanese sufficiently to participate in the interviews;
- 5) Be willing to be audio-recorded during the interview sessions.

Approved

Meeting any of the following criterion will exclude a subject from enrollment into the substudy:

- 1) Unable to complete interview within 10 business days of the Week 52 visit
- 2) Has any clinically relevant medical or psychiatric condition that, in the opinion of the investigator and/or study coordinator, would interfere with the completion of the substudy activities. This includes but is not limited to language, speech, hearing or cognitive disorders that could impact a subject's ability to participate in an interview-based discussion.

#### **Substudy Duration and Substudy Procedures**

Subjects are required to participate in 1 telephone interview, lasting approximately 1 hour. Interviews will be conducted as soon as possible after the week 52 visit, but within 10 business days of the visit.

Subjects enrolled in the clinical trial 20170609 will be approached by clinic staff for recruitment and possible enrollment into this substudy.

At participating sites, randomized subjects that are successfully dosed (may miss up to 1 dose during each phase) with investigational product (DBTP and OLTP) will be provided an option to participate in the qualitative interview substudy and be provided with additional information about the substudy. Clinical site staff will explain the substudy objectives and procedures to the subject and obtain a supplementary written informed consent. The signature process for this informed consent will be the same as the informed consent for the main study.

Once consent has been obtained, the subject ID and site details can be communicated by the site to the interview scheduler from 3H Medi Solutions along with potential dates for the Week 52 visit. The interview scheduler will obtain subject contact information and schedule a tentative date and time for the interview with the participant. 3H Medi Solutions will confirm with the site that the subject has completed study procedures for the Week 52 visit before confirming the interview date and time of the interview with the subject to ensure compliance to the substudy protocol.

The subject must personally sign and date the IRB/IEC-approved substudy informed consent before commencement of substudy-specific procedures. A subject is considered enrolled in the substudy when the investigator decides that



the subject has met the substudy participation criteria and subject has signed and dated the substudy informed consent. The interviewer will not interview the subject until 3H Medi Solutions receives written confirmation from sites of completion of week 52 study procedures.

3H Medi Solutions staff, who are trained and experienced in qualitative data collection, will conduct telephone interviews using a semi-structured interview guide (in local language). Subjects will be interviewed about their pre treatment status and any perceived changes since the start of the open label phase of treatment; ie, from the time they were informed they were being administered Erenumab.

Subjects will be interviewed about the changes experienced and the meaningfulness of the changes experienced. During the interviews, interviewers will ask subjects for specific examples to qualitatively illustrate the subjects' experience.

Subjects will be specifically asked about their experiences with functioning during and between migraine attacks after the start of the open label phase; ie, perceptions of migraine, associated symptoms, and symptom impact/burden and interference on their life; perceptions of meaningful changes in experience of migraine; experience with treatment administration.

After open-ended questions, if subjects do not mention concepts associated with the domains of the COA instrument in the clinical trial, the interviewer will specifically probe about those concepts. The interviewers will also explore what aspects of improvement or worsening of their migraine (eg, frequency, severity, and duration) drove the changes, as well as the meaningfulness of change/no change reported by the subject.

## **Variables**

### **Substudy Outcome Variable(s)**

Qualitative data on changes resulting from treatment received in the open-label extension will be collected via telephone interview. Concepts that emerge from the qualitative interviews in relation to migraine impact, treatment efficacy, and migraine experience will be the outcome. Data will be analyzed to achieve the study objectives, using qualitative data analysis software (ie, ATLAS.ti). Upon

unblinding as outlined in the parent protocol, the clinical trial data may be further used to explore response perceptions.

#### **Exposure Variable(s)**

Subjects will be randomized to placebo or erenumab 70 mg (1:1) SC injections every 4 weeks in the DBTP; during open-label extension of study protocol 20170609, all subjects will receive erenumab 70 mg. Interviewers and subjects will be blinded to the treatment that subjects were administered during the parent clinical trial.

#### **Substudy Sample Size**

The substudy sample size is based on a convenience sample to allow for sufficient numbers of EM and CM subjects enrolled.

The substudy sample will be a subset of up to 40 subjects who will be recruited from up to 6 clinical sites participating in the clinical trial 20170609 across Japan.

#### **Substudy Data Analysis**

Audio recordings from the interviews will be transcribed for qualitative analyses. Evidera will develop a separate data analysis plan that will detail how the qualitative data will be analyzed. The analyses of interview data will help to illustrate subjects' perceptions of meaningful change or difference, migraine functional impacts, and treatment efficacy or benefit. The qualitative report will discuss (1) subject-reported perceptions of migraine, associated symptoms, and symptom impact/burden and interference on subject's life, (2) subject's perceptions of meaningful changes in experience of migraine and (3) subject's experience with treatment administration.

A qualitative content analysis approach will be used to analyze data collected from qualitative interviews using coding dictionaries and ATLAS.ti qualitative data analysis software. The cleaned transcripts will be entered into ATLAS.ti qualitative analysis software version 7.0 or higher (Friese and Ringmayr, 2013). Qualitative data coded in ATLAS.ti can be systematically organized into analysis outputs. ATLAS.ti software is designed to facilitate the storage, coding, and retrieval of qualitative data.

Coding will be an iterative process that marks the beginning of the qualitative analysis process. Concept codes will be used to capture symptoms or impacts of

the disease most important and relevant to participants. Qualitative data will be coded according to the coding dictionary as outlined in the analysis plan. The initial coding dictionary will be based on the structure of the main themes and content of discussion guide to allow the text data to be coded with key concepts codes. The coding dictionary will be iteratively updated with emerging themes and concepts from discussions.

All analysis and reporting will be conducted by Evidera staff with experience in qualitative research.

Subject characteristics collected in the clinical trial will be summarized for describing the sample. Descriptive statistics (eg, n, mean, SD, and/or frequency) will be used to characterize the sample in terms of questionnaire data, sociodemographic, and clinical characteristics.

#### **Collection of Safety Information and Product Complaints**

There will be no substudy specific safety database for collection, recording, and reporting of adverse events reported during the conduct of the substudy. All safety data collection, recording, and reporting will be performed through the parent study and will follow the detailed procedures outlined in study protocol 20170609. Adverse events, serious adverse events, or product complaints reported during the conduct of an interview will be reported to Amgen and to investigational sites within 1 business day of awareness.

#### **Definition of Safety Events**

Refer to Section 9.2.3.1 of the parent protocol for definition of safety events.

#### **Safety Reporting Requirements**

The clinical site Investigator is responsible for ensuring that safety events (adverse events, product complaints, and other safety findings) are reported in accordance with Amgen's clinical trial 20170609 protocol. 3H Medi Solutions will notify the clinical site and Amgen with any report of adverse events to complete the adverse event data collection into the Study 20170609 database. 3H Medi Solutions will report any adverse events to the clinical site and Amgen within 1 business day of awareness; the site Investigator will be responsible for reconciling the reporting to Amgen.

**Safety events must be submitted by the clinical site Investigator as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) which will be the responsibility of the subject's clinic site in accordance with clinical trial 20170609 protocol.**

Approved



- Update language for subject enrollment to clarify that subjects may proceed to the baseline period if Part 1 eligibility criteria is not met, or subjects will be screen-failed if all Part 2 eligibility criteria is not met.
- Remove language that individuals who do not meet the criteria for participation in the study (screen failure) may be rescreened 1 time.
- Add that in addition to weeks 24, 32, 36, 40, 44, and 48, erenumab will also be administered at week 28 during the 28-week open-label treatment period.
- Add that anti-CGRP monoclonal antibody use, including current or prior use, is excluded throughout the study.
- Remove protocol-specific criteria language from reasons for removal from study.
- Add language to describe the [REDACTED]
- Update the volume of blood samples to be collected for measurement of blood concentrations of erenumab as specified in the Schedule of Activities.

- [REDACTED]
- Administrative, typographical, and formatting changes were made throughout the protocol.

Approved